Introduction

Worldwide, more than 284 million people have diabetes, and this number is expected to reach 439 million by 2030. Approximately 90% of these people have type 2 diabetes (T2D), leading to an increasing economic burden upon healthcare systems. Although prevention of T2D is the ideal solution and has been shown to be cost-effective in modeling studies, providing optimal cost-effective treatment to those with T2D is an urgent medical need. Uncontrolled blood glucose leads to microvascular complications and increases the risk of macrovascular complications. These complications have an adverse impact on quality of life (QoL), and their management is a major source of expenditure in people with T2D. Strict glycemic control is required to prevent or delay these complications, thus promoting long-term health and reduced treatment costs.

Glycemic control in T2D is managed initially by diet and lifestyle interventions, followed by use of oral antidiabetic drugs (OADs) and incretin-based therapies. These therapies and their associated costs have been comprehensively reviewed. Historically, insulin-based therapy has been used as a ‘last resort’ in patients with T2D; however, the benefits of earlier initiation of insulin are now generally recognized, including improved glycemic control and reductions in diabetes complications.

The aims of this narrative review are to highlight the importance of health economic (HE) evaluations of T2D treatments in Europe, examine select HE studies in patients with T2D, and provide an assessment of this literature with respect to the HE consequences of treatment intensification. In particular, because questions remain unanswered concerning the best strategies for initiating and managing T2D with insulin therapies and their overall impact on the costs of treatment, we will focus this review on the economic implications of insulin-based therapies in T2D.

Methods

Articles for consideration for this expert opinion review were identified using a PubMed search restricted to English language
publications from 2000 to 2012, using ‘type 2 diabetes mellitus’ or ‘insulin’ (title term) and ‘economics’ (MeSH term). Search outputs were further limited to peer-reviewed articles and those pertaining to EU countries. Following this search, inclusion of data in this article was determined subjectively by the authors based on the relevance to the English-speaking EU prescriber.

**Results**

**Cost of T2D management.** Landmark European studies have shown that treatment of T2D is very costly.\(^5\)\(^7\)\(^8\)\(^13\)\(^16\)

For example, in the T2D Accounting for a Major Resource Demand in Society (T\(^2\)ARDIS; \(n = 1578\)) survey in the UK, the average annual National Health Service (NHS) cost per patient in 2000 was £1738 (€2639),\(^3\) driven primarily by the cost of hospital care (Fig. 1).\(^7\) In this study, patients visited their general practitioners an average of five times a year. Similarly, the Cost of Diabetes Type II in Europe (CODE-2) study, conducted in eight European countries, reported the total annual direct medical costs associated with T2D to be €29 billion (1999 values).\(^13\)

A study commissioned by Diabetes UK reported that, during the decade from 1997 to 2007, the mean prescribing costs for T2D patients increased by 89% (from £391 to £740) prescribing costs per person per year (pppy)\(^4\) and the total costs of primary care rose by 79% (from £602 to £1080 ppppy).\(^4\) For perspective, over the same period, the rate of inflation in the UK was approximately 28%.\(^17\) The increase in diabetes costs was partially due to a doubling in the number of general practitioner consultations (including surgery, home, community clinic visits, and telephone consultations) from 5.4 ppppy in 1997 to 11.5 ppppy in 2007. Despite increased expenditure, glycemic control did not improve over the same period; however, improvements in blood pressure and lipids were noted.\(^4\) By 2010/2011, the total cost of T2D in the UK was estimated to be £8.8 billion.\(^18\)

**Cost of T2D complications.** Diabetes complications are an important cost driver in the overall cost of T2D management.\(^6\)\(^–\)\(^8\)\(^19\)

In the T\(^2\)ARDIS survey, the presence of complications increased the primary care costs 5.6-fold, with microvascular complications leading to a 2.5-fold increase.\(^7\) In the CODE-2 study, 24% of patients had both micro- and macrovascular complications, resulting in a total cost increase of 250% compared with patients who had no complications.\(^4\) For a Spanish population within the CODE-2 study, the presence of both micro- and macrovascular complications increased the mean cost per patient by 142%.\(^20\)

Diabetic drug cost is small compared to the cost of managing T2D complications; for example, in the T\(^2\)ARDIS survey, only 18% of total cost was for insulin and OADs, while almost the same amount (16%) was spent on nondiabetic drugs (largely for treating macrovascular complications) (Fig. 1).\(^7\)

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\(^{16}\)Estimated currency conversion based on average exchange rate in year of study.
Using the IMS-CORE

In addition, hypoglycemia and weight gain are common adverse events with older agents. With the introduction of glucagon-like peptide-1 (GLP-1) analogs and sodium/glucone cotransporter 2 (SGLT2) inhibitors, it is now possible to improve glycemic control and potentially reduce weight when metformin alone is no longer sufficient. A more complete discussion of the cost-effectiveness of combining OADs, incretin therapies, and SGLT2 inhibitors is beyond the scope of this review.

The reduction in severity and/or delayed onset of diabetes complications after achieving more effective blood glucose control using insulin therapy may be cost-effective and result in improved patient QoL. Using the IMS-CORE Diabetes Model applied to data from the UKPDS study, it was estimated that initiating insulin in patients with poor glycemic control immediately versus a delay of eight years would result in a gain of 0.61 years of life expectancy and 0.34 QALYs. These benefits were directly attributable to a delay in onset and reduced cumulative incidence of diabetes complications. An observational German study showed that the total average cost of diabetes care for six months following initiation of insulin rose from €579 to €961, which included costs of blood glucose monitoring and specialist care in addition to the insulin itself. These costs increased significantly more in patients with higher body mass index and A1C, suggesting that delay in insulin initiation may lessen its cost benefits.

Unfortunately, insulin initiation often occurs after prolonged periods of poor control, and a large proportion of patients with T2D using insulin remain poorly controlled. Insulin regimens can reduce complications and increase QoL and survival, but place greater demands on patients and physicians to adjust doses and increase the intensity of blood glucose monitoring. The use of pen injection devices for insulin delivery has been shown to improve compliance and cost-effectiveness compared to vials and syringes. Physicians can also influence compliance with insulin treatment regimens by being positive in their attitudes toward insulin therapy and its benefits.

Recent HE studies have included the assessments of, and comparisons between, a number of insulin therapies, including insulins glargine and detemir (long-acting), insulin aspart (short-acting), biphasic (mixed) insulin, neutral protamine Hagedorn (NPH) insulin (intermediate-acting), and human soluble insulin. The use of insulin analogs has been shown to be more cost-effective compared to human insulin (despite higher drug costs) due to improved glycemic control and reduced propensity for hypoglycemia and weight gain. Differences in cost-effectiveness between the available insulin analogs depend largely on the frequency of hypoglycemia and its associated costs, although a lack of direct drug comparisons makes economic analysis difficult. In lieu of clinical studies,
A separate year-long study in the UK measured 244 episodes of severe hypoglycemia requiring emergency treatment in 160 patients, costing a total of £92,078 (€137,442) and €533 versus €441 in Germany, €691 versus €577 in Spain, and €537 versus €236 in the UK. The UK reported higher treatment costs for patients with T2D exhibiting poor glycemic control the proportion of patients reaching their target without nocturnal hypoglycemia, whereas studies of insulin detemir have reported the proportion of patients reaching targets without any episode of hypoglycemia.

**Conclusions**

Given the rising incidence of T2D and the burden on healthcare services, HE evaluations of the management of T2D are becoming increasingly relevant worldwide. HE studies in numerous countries have shown that hospital inpatient care (mostly due to diabetes complications) accounts for about half of the total expenditure for T2D, while diabetes medication and supplies account for a much smaller percentage. Thus, diabetes complications are not only detrimental to QoL and long-term prognosis but also account for a disproportionate share of the total cost of managing T2D.

Clinical studies have demonstrated that intensification of treatment to achieve stricter glycemic control and thereby reduce or prevent complications may be one of the most cost-effective interventions for T2D patients with inadequate glycemic control. The studies reviewed here suggest that earlier introduction of insulin therapy may be more cost-effective than prescription of multiple oral therapies with or without incretin therapy. However, adverse events associated with insulin therapy, especially hypoglycemia and weight gain, may offset some extent the clinical and economic benefit. Although questions remain as to when to initiate insulin and to what extent one insulin analog may be superior to another, in patients with T2D exhibiting poor glycemic control the data reviewed here suggest that treatment with an insulin analog will improve medical outcomes and is cost-effective.
Earlier introduction of insulin therapy may result in treatment-related adverse events such as hypoglycemia and weight gain associated with insulin. Diabetes complications are an important cost driver. Intensive blood glucose control reduces the cost of treatment with an insulin analog may improve medical outcomes blending ultra-long-acting insulin with a short-acting version may offer better postprandial glycemic control. The potential advantages these agents have over existing basal insulins suggest that they may have an important role to play in future T2D management.

Insulin remains the most effective anti-glycemic therapy in T2D, but the timing of the initiation of insulin treatment is a topic of considerable debate. Earlier use of insulin could reduce and/or delay diabetes complications, which would help cut the largest cost in T2D. It has been argued that initiation of insulin is more resource intensive (particularly in terms of clinician time and overcoming patient reluctance) and thus more expensive to initiate than oral therapies. But given that most patients with T2D will ultimately require insulin, treatment initiation is not likely to be an avoidable cost. If benefit is to be maximized and cost minimized, insulin treatment must be individualized and self-monitored to avoid hypoglycemia and/or weight gain. Use of insulin glargine or detemir rather than NPH insulin may be useful in this regard; both long-acting analogs are associated with fewer episodes of hypoglycemia and insulin detemir with less weight gain. More finely tuned guidance concerning the choice of insulin and the ideal timing of initiation require further research.

Five-year View
The global cost of treating T2D is projected to increase over the next five years, reaching approximately €375 billion by 2030. Minimizing this cost while improving outcomes will be a major challenge. Unfortunately, many individuals remain unable to make the required long-term changes in their behavior and lifestyle despite investment in educational programs. Improvements in outcomes will most likely come from new treatments and better use of existing treatments. In particular, recommendations on the choice of second-line therapy should become clearer in terms of both clinical benefit and cost, and clinical experience with newer agents, such as SGLT2 inhibitors, should provide insight into their place in treatment algorithms.

Earlier insulin initiation may prove more beneficial in the future as new insulin formulations offering better control, fewer adverse events, and easier management of T2D become available. These formulations include ultra-long-acting analogs that have flatter and more consistent metabolic effects and improved adverse event profiles. Insulin degludec, for example, is a novel insulin analog now in clinical use that produces a longer duration of action with varied daily dose timing. In addition, degludec is associated with a lower incidence of hypoglycemia than insulin glargine. Longer duration of action and reduced adverse events have also been achieved by conjugating insulin with polyethylene glycol (PEG) in PEGylated insulin lispro, which is currently in development. In addition, further innovations blending ultra-long-acting insulin with a short-acting version may offer better postprandial glycemic control. The potential advantages these agents have over existing basal insulins suggest that they may have an important role to play in future T2D management.

Key Issues
- Diabetes complications are an important cost driver in T2D management; patients with complications incur costs up to 250% higher than patients without complications.
- The cost of glucose-lowering drug therapy for T2D is small compared with the cost of managing diabetes complications (18% vs 40–60%, respectively, of the total cost).
- Intensive blood glucose control reduces the cost of complications compared to conventional management by more than enough to offset the increase in treatment costs.
- Treatment-related adverse events such as hypoglycemia and weight gain can be associated with significant healthcare costs and reduced QoL.
- Earlier introduction of insulin therapy may result in more effective blood glucose control, a reduction in the severity and/or delayed onset of diabetes complications, and improved patient QoL.
- Hypoglycemia and weight gain associated with insulin therapy may offset to some extent the clinical and economic benefit.
- Both insulin glargine and insulin detemir are associated with a lower frequency of hypoglycemia than NPH insulin; insulin detemir is associated with less weight gain.
- Treatment with an insulin analog may improve medical outcomes and is cost-effective in patients with T2D with poor glycemic control.

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Author Contributions
Agreed the manuscript concept and content structure at project initiation: AL, KK, DOB, JFY. Analyzed the data: AL, KK, DOB, JFY. Wrote the first draft of the manuscript: AL, KK, DOB, JFY, with editorial support from
PAREXEL MMS. Contributed to the writing of the manuscript: AL, KK, DOB, JFY. Agreed with manuscript results and conclusions: AL, KK, DOB, JFY. Jointly developed the structure and arguments for the paper: AL, KK, DOB, JFY. Made critical revisions and approved final version: AL, KK, DOB, JFY. All authors reviewed and approved of the final manuscript.

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