ORIGINAL RESEARCH

Evaluation of Insulin Use and Value for Money in Type 2 Diabetes in the United Kingdom

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ABSTRACT

Introduction: It is unclear as to whether human or long-acting analog insulins

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represent the most efficient use of health and non-healthcare resources in the management of type 2 diabetes mellitus (T2DM). The aim of this study was to evaluate the value for money relationship associated with the use of these insulins in the UK setting.

Methods: A literature search was performed for studies reporting expenditure associated with the use of human and analog insulins. Data from this review informed a budget impact assessment model. Costs were converted to a common currency and results are reported in 2011 British pounds sterling (GBP) values.

Results: Annual diabetes-related medication expenditure and patients total expenditure associated with the management of T2DM were estimated to be £397 million and £3,901 million, respectively. Substitution of human insulin for analog insulins was associated with a drug acquisition cost saving of between £5 million and £23 million each year. Overall, though, total expenditure increased significantly with increased use of human insulin by £34 million to £136 million each year depending on the degree of substitution.

Conclusions: On the face of it, analog insulins are more expensive, prompting questions about potential cost savings to health services in the UK from direct substitution to the less

expensive human preparation. The current analysis illustrates that the increased use of human insulin and decreased use of analog insulin would, however, increase the overall net societal cost of managing insulin-treated patients with T2DM. Governments and decision makers should consider that total healthcare expenditure would not necessarily fall when decisions are based solely on the use of cheaper products.

Keywords: Costs and cost analysis; Diabetes mellitus; Human insulin; Insulin analog; Resource allocation; Type 2 diabetes

INTRODUCTION

Background

There are an estimated 346 million people with diabetes worldwide. Type 2 diabetes mellitus (T2DM) is the most common, accounting for 90% of the diabetic population [1]. Unlike people with type 1 diabetes, who require insulin, people with T2DM can initially manage their condition without pharmacological intervention. However, the natural history of T2DM, characterized by progressive decline in beta cell function, results in an inevitable need for multiple pharmacotherapies including oral antidiabetic drugs (OADs), insulin, or both, in order to optimize blood glucose control [2]. Indeed, over the course of the UK Prospective Diabetes Study (UKPDS), >50% people treated with sulfonylureas required additional insulin to maintain fasting plasma glucose levels <6 mmol/L, within 6 years of T2DM diagnosis [3].

There is a growing emphasis on insulin management. Insulin initiation early within the natural history of T2DM is now endorsed by professional bodies including the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) [4]. The growing prevalence of T2DM and data suggesting a reduction in mortality in people with T2DM indicate that the use of insulin for the management of glucose control in people with T2DM will continue to rise [5].

Accordingly, there is widespread interest in evaluating the safety, efficacy, cost-effectiveness, and affordability of alternative insulin treatments. A number of insulin products are available that address variability in patient phenotypes, preference, and response to treatment. Preparations are available that more closely mimic normal insulin production (short-acting) or provide a continuous supply of insulin over a longer time period (intermediate- and long-acting).

Recent Evidence

The intermediate-acting human isophane insulin (NPH) and the long-acting analog insulins glargine and detemir have been the subject of recent reviews that have brought into question the clinical benefits and economic value of long-acting insulin analogs compared to human insulin [6–8]. These reviews suggest that insulin analogs and NPH are similarly effective in terms of glycemic control; however, clinical and economic value should also be assessed from the perspective of other clinical endpoints, including hypoglycemia [9]. Hypoglycemia is a recognized consequence of intensification of glucose control [10–12]. In people with T2DM receiving insulin therapy for <2 years, nearly 50% of patients reported recurrent symptomatic hypoglycemia, while 20% of patients reported at least one episode of severe hypoglycemia [13]. Hypoglycemia has significant clinical and economic implications, thus an increase in the rate of hypoglycemia with human compared to analog insulin may

exert significant health economic implications [14–17]. Further, it is important to remember that these reviews were based on the results of randomized controlled trials that evaluated highly selected patient populations under tightly controlled conditions [6, 7]. As such, these conclusions may not truly reflect patient outcomes as observed in clinical practice nor reflect the actual value of human insulin compared to analog insulin.

Nonetheless, a natural question arising from these reviews is whether health systems could achieve productivity savings from switching to human insulin. A recent analysis characterizing patterns of insulin prescriptions suggested that the UK National Health Service (NHS) would have achieved savings of £635 million from 2000 to 2009, had all prescriptions been for human insulin [8]. Thus, on the face of it, starting people with T2DM on human insulin or even converting people from analog insulin may reduce health expenditure. However, there are other relevant considerations when informing decisions around the optimization of health spending and medication choice in the treatment of T2DM.

Acquisition Costs and Total Expenditure

A comparison of product acquisition costs alone, that is the cost of prescribed medications to the NHS, fails to address the much larger set of costs associated with the management of T2DM. The other parameters that should be considered in a value for money evaluation include both direct and indirect costs. The direct costs for diabetes patients include publicly funded healthcare, most often in terms of primary and secondary care, prescribed medications, and other treatments. The indirect costs incurred by patients, their families, and caregivers include time spent in

managing the symptoms of T2DM and adjusting their lifestyles to the needs of the condition; for example, they incur out-of-pocket expenses associated with transport to healthcare services and in paying for specialist foods used to regulate metabolic activity. When the full spectrum of cost is considered, then medication costs, OADs, and insulin account for only 7% of total healthcare expenditure in the management of T2DM, while diabetes-related late complications and hospitalizations are the single greatest determinant of costs [18]. Hence, from the perspective of informing public spending decisions, an evaluation of acquisition costs alone does not provide a true sense of the total economic consequences associated with insulin choice.

Aims

The purpose of this study was to extend the analysis of human versus analog basal insulin to illustrate the limitations of analyses that, we argue, improperly restrict the decision context to the results of randomized trials and drug acquisition cost. We aim to inform questions surrounding the "value for money" associated with the use of human and long-acting analog insulins.

MATERIALS AND METHODS

Literature Review

The authors adopted a societal perspective by considering the direct and indirect costs associated with T2DM. The authors developed a prevalence-based budget impact assessment model that characterizes components of resource utilization (costs) associated with the periods surrounding insulin initiation, defined by the need for resources used in the

management of T2DM. Evidence informing the budget impact model came from a literature search of PubMed using the keywords: "human insulin" OR "NPH" OR "glargine" OR "detemir" AND "cost" OR "resource utilization". Study titles and abstracts were first reviewed followed by complete manuscripts. Included studies were from 2006 onwards, an arbitrary cut-off to help ensure extracted data reflected contemporary clinical practice. The authors did not have access to a translation service and so only studies written in the English language were considered. Studies had to describe resource use (costs) associated with the use of human and analog insulin or either insulin alone. Data on total costs and cost components were extracted from each included study. Economic modeling studies were excluded as it was anticipated that the primary data contained in economic modeling studies could not be extracted readily or consistently.

Data from the reviewed studies was summarized for human insulin and long-acting analog insulins. The results for the human and analog insulins were stratified according to whether they were direct costs: hypoglycemia-related, medications (diabetes or other), medical services (diabetes or other); or indirect costs.

Analytical Approach

Data from the included studies was summarized for each direct and indirect resource category associated with the management of T2DM and use of basal insulin. Data for total expenditure and diabetes-related medication expenditure were adjusted to 2011 values and standardized to British pounds sterling (GBP) in references to temporal changes in country exchange rates [19]. A quasi meta-analysis was undertaken whereby the point estimates from each study were weighted by the proportion of subjects in each insulin group. A full meta-analysis was not permitted, as the included studies did not consistently report variation around mean estimates. The data included in the analyses originated from several countries; to reflect the UK setting an adjustment was made in the budget impact calculations by scaling study estimates by the ratio of total healthcare expenditure as a percentage of output [gross domestic product (GDP)] in the UK to total healthcare expenditure as a percentage of GDP in the other country. Values obtained from published sources indicated the US spends 16.0% of its total GDP on healthcare, Germany 10.4%, and the UK 8.4% [20]. Point estimates for annual diabetes-related medication expenditure and total expenditure were obtained by multiplying annualized per-person estimates of expenditure by estimates of the prevalence of T2DM in the UK, the proportion of the prevalent population using insulin therapy, and the proportion of people prescribed human and analog insulin.

RESULTS

Literature Review

The literature review identified 161 studies and a variety of resource utilization categories (Table 1). Of the reviewed studies nine were considered relevant (Tables 2, 3) [14, 21–28]. All studies were industry-sponsored. Details of the included studies including number of people, treatment setting, study year, study design and follow-up period, mean age, and primary objective, are reported in Table 4 [14, 21–28].

Budget Impact Assessment

In the budget impact assessment, total diabetes-related medication expenditure per person was

Table 1 Categories of resource utilization

Direct costs

  Hypoglycemia treatments

    Sweet food

    Sweet drinks

    Glucose

    Glucagon

  Training and education

    Diabetes management (incl. DSN)

    Leaflets

    Hypoglycemia awareness

    Psychological counselling

  Medications

    Diabetes related (OADs, insulin)

    Nondiabetes

  A1c testing

    SMBG

  Ambulance service—callouts and carries

    Diabetes related

    Nondiabetes

  Emergency room visits

    Diabetes related

    Nondiabetes

  Inpatient admissions

    Diabetes related

    Nondiabetes

  Outpatient services

    Endocrinologist

    Diabetologist

    General practitioner

    Other

Indirect costs

  Family/carer time

  Time off work

  Co-payments

A1c glycated hemoglobin, *DSN* diabetes specialist nurse, *OADs* oral antidiabetic drugs, *SMBG* self-monitoring blood glucose

15% lower each year with human insulin versus analog insulin. Once all relevant costs were factored into the analysis, the total annual expenditure associated with human insulin was 8% higher at an individual level compared to analog insulin, and this includes the cost of diabetes-related medications.

The authors estimate that for the UK-prevalent population of T2DM, patients total and diabetes-related medication expenditure is £3,901 and £397 million, respectively, each year. The authors estimate that medication acquisition cost savings in the order of £26 million a year might be achieved if all analog insulin users converted to human insulin, but that any savings in medication acquisition cost would be consumed/offset by the estimated increase in overall treatment costs to individuals and the NHS of £284 million each year.

Across modeled scenarios whereby there is a positive utilization of each insulin type, a 10% increased use of human insulin and a proportional decrease in the use of long-acting analog insulin would save the NHS around £5 million each year on drug acquisition cost, but the net overall cost to the NHS would increase by £34 million each year (Table 5 [1, 6, 8, 29], Fig. 1). For scenarios ranging from a 10% to 40% increased use of human insulin and an equivalent reduction in the use of analog insulins from current levels, this equates to a potential saving between £5 million and £23 million each year on drug acquisition cost, but the net overall cost to the NHS would increase by £34 million to £136 million each year.

DISCUSSION

In the management of T2DM a complicated picture arises when considering the relationship between overall clinical benefit (for example, glycemic control vs. hypoglycemia), treatment options (comparative effectiveness), and

Table 2 Details of studies of human insulin (per patient per annum, 2011 GBP)

	Study						
	Rhoads [21]	Lee [22][a]	Schoffski [23][b]	Brod [14][c]	Hammer et al. [27]/ Lammert et al. [28][d]	Range (LL)[e]	Range (UL)[e]
Diabetes-related costs							
Hypoglycemia related	–	–	–	–	1,069	1,069	1,069
Medications/ associated devices	–	1,460	1,694	–	–	1,460	1,694
Medical costs	–	1,617	–	–	–	1,617	1,617
Indirect costs	–	–	10	1,186	35	10	1,186
Total	5,493	3,076	–	–	–	3,076	5,493
Total costs							
Medications	–	5,875	1,949	–	–	1,949	5,875
Medical costs	–	14,803	802	–	–	802	14,803
Indirect costs	–	–	10	1,186	–	10	1,186
Total	18,347	20,679	2,761	–	–	2,761	20,679

Weighted average across three treatment settings which were defined as the severe event being treated and managed by a "family member/friend", "community healthcare worker" or "in hospital"

Historical exchange rates used for conversion [19]

GBP British pounds sterling, *GDP* gross domestic product, *LL* lower limit, *OADs* oral antidiabetic drugs, *UL* upper limit

[a] Values based on estimates post-insulin initiation, annualized

[b] Including insulins, OADs, blood glucose self-testing devices, pens and needles required for insulin administration

[c] Multi-country study of type 1 and 2 diabetes. Values refer to type 2 population only

[d] Multi-country study, UK data reported

[e] Data are point estimate (mean) values. Range refers to spread of mean values across included studies before adjustment for variation in GDP per country or study size

consequent direct healthcare expenditure and indirect costs. Many clinical studies—randomized and observational—have attempted to address the effectiveness and comparative effectiveness of technologies used in the management of T2DM [6, 30]. Certainly, many individual studies, mostly observational in nature, have often addressed narrow and disparate research questions about the financial costs associated with the management of T2DM. The aim of this study was to provide an understanding of the likely expenditure associated with T2DM and the use of different basal insulin products across patients, their families, health services, and society.

Comparison to Other Studies

In the UK it has been estimated that around £3.5 billion is spent on diabetes each year [31, 32]. Looking across the various levels of a health service and more broadly into society, the authors estimate the total expenditure associated with T2DM to be £3.9 billion each year. Our analysis of human and analog insulins suggests that total annual diabetes-related medication expenditure is £397 million.

This analysis extends recent reports of the value for money relationship between human and analog insulins by delineating medication acquisition costs and total costs associated with

Table 3 Details of studies of analog insulins (per patient per annum, 2011 GBP)

	Study									
	Rhoads [21]	Lee [22][a]	Schoffski [23][b]	Pscherer [24]	Bretzel [25]	Borah [26][c]	Brod [14][d]	Hammer et al. [27]/ Lammert et al. [28][e]	Range (LL)[f]	Range (UL)[f]
Diabetes-related costs										
Hypoglycemia related	–	–	–	–	–	–	–	1,069	1,069	1,069
Medications/ associated devices	–	1,813	1,325	1,205	1,224	2,700	–	–	1,205	2,700
Medical costs	–	831	–	–	–	3,196	–	–	831	3,196
Indirect costs	–		0	–	–	–	1,186	35	0	1,186
Total	5,253	2,644	–	–	–	–	–	–	2,644	5,253
Total costs										
Medications	–	5,993	1,760	–	–	6,758	–	–	1,760	6,758
Medical costs	–	11,813	739	–	–	8,052	–	–	739	11,813
Indirect costs	–	–	0	–	–	–	1,186	–	0	1,186
Total	16,576	17,806	2,499	–	–	15,854	–	–	2,499	17,806

Weighted average across three treatment settings which were defined as the severe event being treated and managed by a "family member/friend", "community healthcare worker" or "in hospital"

Historical exchange rates used for conversion [19]

GBP British pounds sterling, *GDP* gross domestic product, *LL* lower limit, *OADs* oral antidiabetic drugs, *UL* upper limit

[a] Values based on estimates post insulin initiation, annualized

[b] Including insulins, OADs, blood glucose self-testing devices, pens and needles required for insulin administration

[c] 180 day follow-up period, annualized

[d] Multi-country study of type 1 and 2 diabetes. Values refer to type 2 population only

[e] Multi-country study, UK data reported

[f] Data are point estimate (mean) values. Range refers to spread of mean values across included studies before adjustment for variation in GDP per country or study size

human versus analog insulin use in the UK. This analysis suggests the maximum total cost saving if all users of analog insulin switched to human insulin would be around £260 million over a 10-year period, less than half (41%) of recent estimates suggesting total cost savings over the last 10 years might have been in the region of £635 million [8]. Furthermore, the authors show that any cost saving associated with the acquisition cost of the relatively less expensive

human insulin is outweighed by the utilization of other healthcare resources and indirect costs.

Limitations

There are a number of limitations of this research that may impact the interpretation of the authors findings. Firstly, in restricting the literature search to recent studies in English and by excluding economic modeling studies there

Table 4 Details of studies and patient characteristics identified from the literature review

Author	No. of people	Treatment setting	Study year[a]	Study design/ follow-up period	Age (mean)	Therapy	Primary objective
Rhoads [21]	Glargine: 2,105 NPH: 734	30 managed healthcare plans across the US	2011	Retrospective analysis of claims data Data collected during 2001–2005	54.6 (both groups)	Oral agents only in the pre-index period Glargine or NPH insulin post-index	To compare 2-year glycemic control, hypoglycemia, and healthcare expenditures following insulin glargine or neutral protamine hagedorn (NPH) insulin intiation in patients with type 2 diabetes
Lee [22]	Glargine: 1,698 NPH: 400 (analysis based on 400 matched pairs)	31 self-insured companies in the US	2010	Retrospective analysis of claims data Data collected during Oct 2001 through June 2005	Glargine: 52.9 NPH: 53.8	Previously insulin naïve initiating glargine or NPH insulin	To compare total costs and risk of hypoglycemia in patients with type 2 diabetes initiated on NPH insulin versus glargine in a real-world setting
Schoffski [23]	512 (for each group)	Germany	2008	Observational, longitudinal, multicenter ($n = 20$), cost comparison using physician databases	Glargine: 62.5 NPH: 60.6	Insulin glargine or NPH with or without oral agents	To assess and compare the total costs relevant to diabetes care in patients with type 2 diabetes treated at specialized diabetes practices with either insulin glargine or NPH

Table 4 continued

Author	No. of people	Treatment setting	Study year[a]	Study design/ follow-up period	Age (mean)	Therapy	Primary objective
Pscherer [24]	291 (for each cohort)	Germany	2010	Multicenter, randomized, controlled trial	Detemir: 59 Glargine: 58	Insulin detemir or glargine with oral agents	Comparison of 1-year costs of type 2 diabetes treatment with insulin glargine or insulin detemir with oral agents
Bretzel [25]	205	Germany	2009	Multicenter, randomized, controlled trial Main trial follow-up period was 44 weeks for the primary endpoint	60.0	Insulin glargine	A cost analysis of once-daily insulin glargine versus three-times daily insulin lispro in combination with OADs for insulin-naive type 2 diabetes patients
Borah [26]	Detemir: 48 Glargine: 248	A US managed care organization	2009	Retrospective cohort analysis of healthcare claims data and laboratory results Data collected between May 1, 2006 and December 31, 2006	Detemir: 53.9 Glargine: 53.6	Previously insulin-naive patients initiating glargine or NPH insulin	To compare daily insulin use, glycemic control, and healthcare costs in insulin-naive patients with type 2 diabetes who initiated treatment with either insulin detemir or insulin glargine
Brod [14]	691	Multi-country survey: US, UK, Germany, and France	2011	Internet-based survey	42.4	Insulin with or without oral agents (usual management)	To identify how NSHEs in a working population affect productivity, costs, and self-management behaviors

Table 4 continued

Author	No. of people	Treatment setting	Study year[a]	Study design/follow-up period	Age (mean)	Therapy	Primary objective
Hammer/Lammert [27, 28]	100 (50/25/25 by setting)	Managed/treated: 1. family/friends 2. community practitioner 3. in hospital UK data are reported	2009	Retrospective questionnaire Resources consumed during treatment of SHE and until full recovery	By setting: 59.4 58.2 65.7	Insulin with or without oral agents	Investigate the characteristics of people with insulin-treated diabetes, who have experienced SHEs

NPH neutral protamine Hagedorn, *NSHE* nonsevere hypoglycemic event, *OADs* oral antidiabetic drugs, *SHE* severe hypoglycemic event
[a] Year of publication

is a chance the authors have excluded potentially relevant studies from their estimations. Secondly, a full meta-analysis was not possible because the studies identified from the literature review did not consistently report variation around point estimates [only two of the nine studies reported estimates of variation, i.e., standard deviation (SD) or standard error (SE)]. Thus it was not possible to estimate the statistical heterogeneity between studies and therefore their similarity. In using a weighted average of point estimates, with study size as the weighting factor, we are able to quantify the cost implications associated with insulin use, which may be useful to other researchers and decision makers. The authors do stress, however, that caution should be exercised when interpreting their findings given that there may be important differences between the combined studies; the table of study details (Table 4) may be useful in addressing this limitation. Thirdly, the nature of study sponsorship (i.e., industry-sponsored research) may impact the results of an individual study and hence the synthesis of estimates across studies. One approach in addressing this type of bias is to exclude studies whose sponsorship may directly or indirectly affect study findings. The studies identified from the current literature review were all industry-sponsored. On this basis, the authors could not exclude industry-sponsored studies. The authors note this as a limitation of the available data and a potential source of bias in their study estimates.

Cost Drivers

Since the primary therapeutic advantage of the analog insulins relates to a reduction in hypoglycemia [33], potential cost drivers in this context include excess blood glucose monitoring costs [14], additional costs related

Table 5 Estimates of annual costs associated with type 2 diabetes and the use of human insulin and analog insulin (2011 GBP)

Total expenditure analysis (% human/% analog):	Medications used in the treatment of diabetes	Total expenditure (including diabetes-related medications)
	Point estimate	Point estimate
Current split: 39%/59%[a]	396,706,590	3,900,853,530
Hypothetical: 100%/0% (all human)	370,629,000	4,185,102,600
Difference (all human vs. current utilization)	−26,077,590	284,249,070

Point estimates and % change in budget position in moving from 40%/60% (human/analog) to:	Diabetes medications (0% = budget neutral)	Total expenditure (0% = budget neutral)
20/80	416,039,400 (2.81%)	3,913,174,440 (−1.71%)
30/70	410,363,100 (1.40%)	3,947,165,460 (−0.85%)
40/60 (current split 39%/59%)[a]	**404,686,800 (0%)**	**3,981,156,480 (0%)**
50/50	399,010,500 (−1.40%)	4,015,147,500 (0.85%)
60/40	393,334,200 (−2.81%)	4,049,138,520 (1.71%)
70/30	387,657,900 (−4.21%)	4,083,129,540 (2.56%)
80/20	381,981,600 (−5.61%)	4,117,120,560 (3.42%)

Estimates based on 2.8 million people in the UK with diabetes [1, 8], with 90% of people with type 2 diabetes, [1] and 26–27% of these people using insulin [29]

GDP gross domestic product

[a] Average prescription utilization in the UK from 2000 to 2009 [6]. Data are adjusted for study size and variation in GDP per country (see "Materials and Methods" section)
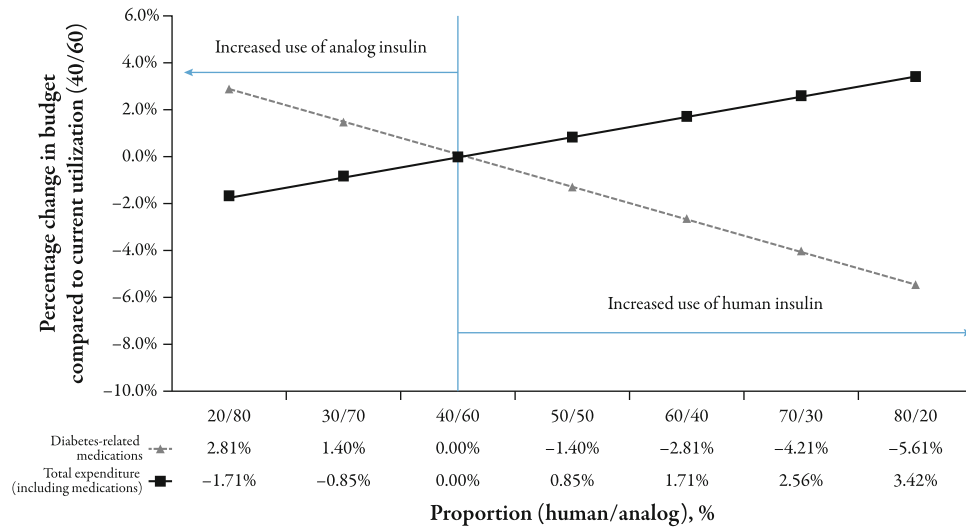
Fig. 1 Budget impact associated with increased use of human/analog insulin (2011 GBP)

to suboptimal insulin dosing and therapy nonadherence consequent upon hypoglycemia [34], and the costs associated with hypoglycemia-associated hospitalization [15, 35, 36]. In explaining why the more expensive long-acting insulin products can be cost saving in terms of total expenditure, the authors speculate to the association between the use of analog insulins and cost offsets associated with a reduction in hypoglycemic events and reduced frequency of injections from twice to once daily.

Hypoglycemia represents a major clinical barrier to achieving glycemic control in people with diabetes and has a major economic impact on overall healthcare spending. Over 30% of people with T2DM treated with insulin experience symptomatic hypoglycemia [37], while data from recent mega trials evaluating the potential outcome benefit associated with intensification of glucose control has demonstrated an association between severe hypoglycemia and an increased risk of diabetes-related complications [38]. Furthermore, a recent retrospective observational analysis of >860,000 people with T2DM which examined

the relationship between hypoglycemic events and acute cardiovascular events over a 2-year period demonstrated that after controlling for multiple confounders, patients with documented outpatient hypoglycemic events had a 79% higher regression-adjusted odds [odds ratio 1.79; confidence interval (CI) 1.69–1.89] of acute cardiovascular events than patients without documented hypoglycemic events. In addition, those patients who experienced hypoglycemia incurred twofold greater health-related expenditure [15]. Further studies are required to confirm these findings.

Hypoglycemia results in significant resource utilization form a healthcare perspective. This concept is supported by the fact that hypoglycemia is the primary diagnosis resulting in 14,437 hospital admissions in the UK between 2009 and 2010, accounting for a total bed occupancy of 76,569 days [39].

Hypoglycemia also has a significant impact on the quality of life of people with diabetes as well as therapy adherence. Symptomatic hypoglycemia is associated with reduced therapy adherence, treatment satisfaction, and

results in many people intentionally maintaining a state of hyperglycemia, with people with T2DM reducing their insulin dose 57.5% of the time following severe hypoglycemia, and 43.0% of the time following mild or moderate hypoglycemia [16, 17, 40, 41]. Indeed, fear of hypoglycemia in younger people with type 1 diabetes is greater than the fear of developing the later complications of diabetes [42]; it is possible that this relationship could carryover to people with T2DM.

A reduction in the frequency of nocturnal hypoglycemia is one the key advantages of the insulin analogs (insulin detemir and insulin glargine), compared to human insulin. This represents a major consideration when considering the value for money proposition of these insulin preparations since almost 50% of all episodes of severe hypoglycemia occur at night during sleep [43]. Nocturnal hypoglycemia results in significant detrimental effects on mood and wellbeing the following day and has the greatest socioeconomic consequences from the perspective of reduced productivity and lost time at work, and represents a particular barrier to optimal insulin dose titration [14, 43, 44]. In addition, nocturnal hypoglycemia has been causally associated with acute sudden death [45], while recurrent nocturnal hypoglycemia is linked to the development of hypoglycemia unawareness, which in turn is associated with a higher rate of severe hypoglycemia [46].

Differences in rates of hypoglycemia between human and analog insulins were conflated in the results of the individual studies that informed our cost analysis. In the discussion the authors have only speculated to theoretically plausible clinical explanations of cost drivers. As such, we cannot directly attribute our expenditure estimates to different cost drivers. Instead we have used a linked evidence approach [47] to highlight the likely role of hypoglycemia as an overall cost driver and explanation for our key finding that human insulin is, on balance, likely to be more expensive than analog insulins.

CONCLUSIONS

It is difficult to gain a sense of the extent of expenditure made by individuals and governments in managing T2DM. The authors find that direct and indirect expenditure is significant. Diabetes-related medication expenditure is generally lower in users of human insulin compared to users of long-acting analog insulin. Overall, though, the use of analog insulins was cost saving compared to human insulin. These productivity gains may be related to fewer hypoglycemic events.

The value for money of human insulin and analog insulins does not rest at medication acquisition costs alone. Governments and decision makers should consider that total healthcare expenditure will not necessarily decrease when decisions are based solely on the use of cheaper products. By factoring in the clinical benefits of insulin analogs in contrast to their higher costs, we estimate that a paradigm shift towards increased use of human insulin and decreased use of analog insulin would on average increase the net societal cost of managing insulin-treated patients with T2DM.

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Conflict of interest. JG, ME, PM, SB, and JV have received payment for lectures and consulting services to manufacturers of insulin products including Sanofi and Novo Nordisk. JG is an employee of HEOR Pty Ltd, and PM is an employee of HEOR Ltd.

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