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Systematic Review

A Systematic Review of Economic Evaluations of Insulin for the Management of Type 2 Diabetes

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Abstract: Diabetes is a chronic, metabolic disease characterized by hyperglycemia, which occurs as a result of inadequate production or utilization of insulin. Type 2 diabetes (T2D) is the most common type of diabetes with estimates projecting a prevalence of more than 1 billion people living with T2DM by 2050. Hence, it was decided to conduct a systematic literature review of health economic evaluations of insulin, the most common medication used for the treatment of the disease, to inform policy. Pharmacoeconomic analyses, written in English and published after 2016, were considered for inclusion. PubMed/Medline, Global Health, Embase and Health Management Consortium were searched separately between 5 July 2023 and 17 July 2023. Grey literature articles were searched on ISPOR and the Cost-Effectiveness Analysis Registry during the same period. After the exclusion criteria were applied, 21 studies were included. Using the BMJ checklist, a quality appraisal was performed on all included studies. Data extraction was performed manually. Regarding evidence synthesis, data were heterogenous and are presented based on study type. The results showed a variety of treatment combinations being available for the treatment of diabetes, with insulin degludec/DegLira and semaglutide being cost-effective despite their high cost, due to the effectiveness of managing the disease. Research around the cost-effectiveness or cost-utility of insulin has potential to progress further, to ensure informed policy-making in the future.

Keywords: systematic literature review; cost-effectiveness; cost-utility; diabetes; insulin; pharmacoeconomics

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1. Introduction

Diabetes is a chronic metabolic disorder, caused by defects in insulin secretion and/or insulin action, which results in hyperglycemia; prolonged hyperglycemia can lead to acute complications (e.g., diabetic ketoacidosis), chronic complications (e.g., retinopathy, chronic kidney damage, diabetic foot ulcers) and, consequently, impaired quality of life (QOL) and reduced life-expectancy [1–3]. Over 500 million people were living with diabetes in 2021, with 96% of cases being Type 2 (T2D); T2D is associated with β-cell dysfunction, insulin resistance, and the impairment of incretin signaling, and prevalence is projected to increase to 1.31 billion people worldwide by 2050 [2,4].

Attaining recommended glycaemic targets, a hemoglobin A1c (HbA1c) of around 53 mmol/mol (7%), which is the average blood glucose level over 3 months, results in the substantial reduction in the onset and progression of macrovascular (e.g., coronary heart disease, cerebrovascular disease) and microvascular (e.g., diabetic nephropathy, retinopathy) complications [5–9]. Time-in-range (TIR), i.e., the amount of time (%) that an

individual's glucose level remains within the proposed target range, should be more than 70% a day to ensure micro- and macrovascular protection. Other useful clinical targets in terms of preventing/well-managing complications are time below range (TBR) and glycemic variability (GV) [10].

Insulin therapy has been the main treatment option for patients with T2D for over a century and it is ultimately required in the chronic management of T2D, if glycaemic targets are not achieved following dietary intervention, review of physical activity behaviour, and oral anti-hyperglycaemic medication [5,11]. There is often a delay in commencing insulin therapy, due to hesitancy both among patients to take insulin and healthcare providers to prescribe [12]; a survey of 66,000 patients found that average HbA1c was 80 mmol/mol at the start of insulin therapy and over 90% of participants already had associated complications [13]. The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) advocate for early introduction of insulin when glycaemic measurements do not meet targets [5].

Insulin is available in numerous formulations (e.g., rapid-acting, short-acting, intermediate-acting, long-acting) to enable the dose and timing to be matched to an individual's physiological requirements [11]. The global median government procurement price for a standardised 100 U/10 mL vial of human insulin is USD 5, compared to long-lasting 'analogue' insulin at USD 33; the individual pays USD 9 for human insulin at pharmacies and private hospitals [14]. That said, the reimbursement environment and guidelines vary significantly on the national level. In 2022, the global insulin market was valued at approximately USD 20.18 billion; yet, it is estimated that 60% of users lack secure access to affordable insulin [15,16].

There are significant costs associated with diabetes and its complications; in 2021 health expenditures were USD 966 billion globally and are forecast to reach over USD 1054 billion by 2045 [4]. Diabetic peripheral neuropathy alone is estimated to cost USD 10.9 billion per year in the United States, whilst diabetic ulceration and amputation costs the United Kingdom's National Health Service up to GBP 962 million annually [17,18]. By 2030, the global economic burden of diabetes and its complications is estimated to reach USD 2.1 trillion, a 61% rise from 2015, even if countries meet the Sustainable Development Goal of decreasing mortality from diabetes by one third [19].

In addition to the financial burden, the rising prevalence of T2D is a major concern as the condition is associated with a serious deterioration in general QOL [20]; T2D was ranked as the seventh leading cause of DALYs (Disability-Adjusted Life Years) in 2017 [21]. Bearing all this in mind, the aim of this study is to conduct a systematic literature review (SLR) on pharmacoeconomic evaluations of insulin in the management of T2D at a global level.

2. Materials and Methods

The databases, PubMed/Medline, Global Health, Embase and Health Management Consortium, were systematically searched for medical subjects, while manual searching was conducted on ISPOR (The International Society for Pharmacoeconomics and Outcomes Research) and the Cost-Effectiveness Analysis Registry to include grey literature in order to reduce bias [22,23]. Each database and website was searched separately between 5 July 2023 and 17 July 2023. The following key-words were used: (diabetes) AND (insulin) AND (econom* OR economic evaluation). The comprehensive search strategy is included in Appendix A.

The inclusion and exclusion criteria were informed by the PICOS search framework (Table 1). Cost-Effectiveness Analyses (CEA) and Cost-Utility Analyses (CUA) were considered for inclusion, based on the criteria outlined below. Published peer-reviewed SLRs were utilized to confirm that the correct methods were used and the appropriate results were included.

Table 1. The PICOS search framework used to inform the inclusion and exclusion criteria within the study.

Population	Intervention	Comparator	Outcome	Study Design
Patients with T2D *	Insulin	Insulin or other pharmaceutical products	Effectiveness and cost-effectiveness in the management of T2D *	CEA [1] CUA [2]

* T2D—type 2 diabetes; [1] CEA—cost-effectiveness analysis; [2] CUA—cost-utility analysis.

During the process of screening, studies written in English, CEAs and CUAs of insulin in the management of T2D and comparisons of insulin products against other insulin products or pharmaceutical products used for the management of T2D were considered for inclusion. Moreover, studies published between 2016 and July 2023 and using data after 2016 were also deemed appropriate. Including studies that had been published before 2016 may have led to inclusion of out-of-date data, as the reimbursement and health economics environment changes regularly, e.g., in the United Kingdom, drug prices are negotiated every 5 years [24]. The inclusion criteria also included real-world studies, as well as grey literature reports and publications by non-industry organisations, to minimise bias. Studies not written in English, published before 2016 or using data before 2016 and not pertaining to insulin, were excluded. Studies with participants aged <18 years, pertaining to any other disease than T2D (T1D, gestational diabetes, cardiovascular diseases), comparing devices or non-pharmaceutical interventions (e.g., exercise) in the management of diabetes, as well as studies on insulin biosimilars, did not meet the inclusion criteria. Finally, reviews, opinions, SLRs, scoping reviews, cohort studies and case-reports were also excluded.

The search for publications was performed independently by two authors (E.G., A.F.), and all retrieved articles were compared to avoid duplication. Any disagreements were discussed, whilst potential conflicts were then solved by a third reviewer (A.B.). The SLR was performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [25]. The titles and abstracts of all studies were screened based on the eligibility criteria by two independent reviewers (E.G., A.F.) and there was 100% agreement between them. Full-text screening was conducted by the two reviewers (E.G., A.F.) for studies that seemed suitable at the abstract and title screening stage or when the title and abstract did not provide enough information. There was 85% agreement between the two reviewers, and a third reviewer (A.B) solved conflicts between them.

For citations published as abstracts that were eligible for inclusion, we attempted to contact the first and/or last author to ask for raw data and/or potential full-text publications. This was applied on 14 ISPOR abstracts, out of which, we identified email addresses for eight authors by searching PubMed/Medline and Google Scholar. However, we did not receive any relevant answers in the 2-week pre-specified deadline. Thus, we believe, the choice to exclude them was justified.

To enhance the reliability and relevance of the review at hand, each study was evaluated for its quality and bias using specific and recognised tools. The health economic evaluations were assessed based on the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement and the British Medical Journal (BMJ) checklist for economic evaluations [26,27]. Each analysis was then scored based on the BMJ checklist with a maximum score of 35, while also considering the CHEERS statement. If an analysis had a score of less than 30/35, it was excluded. By scoring each analysis, it was possible to ensure the inclusion of studies with robust results and minimised bias.

Data extraction was performed manually using extraction forms created on Microsoft Excel 360. The following data were extracted from each included study: last name of first author, year of publication, country/ethnicity, sample size/number of patients and controls (where applicable), study inclusion/exclusion criteria, analysis type, type of comparison (insulin vs. insulin or insulin vs. other pharmaceutical products) and additional comments (if applicable). Considering selection heterogeneity across studies, a meta-analysis could not have been conducted. Therefore, the results were grouped based on study type (CEA,

CUA) on the first level and based on comparison (insulin vs. insulin or insulin vs. other pharmaceutical interventions) on the second level.

3. Results

3.1. PRISMA Flowchart

The database search yielded 7745 citations in total, of which, 2301 were duplicates and were excluded. Manual searching identified 23 results, of which 100% were duplicates with the results on the medical databases being consequently excluded, with 2324 duplicates being removed in total. The steps of the study selection, along with the reasons for the exclusion of full texts, are presented in the PRISMA flow diagram (Figure 1).

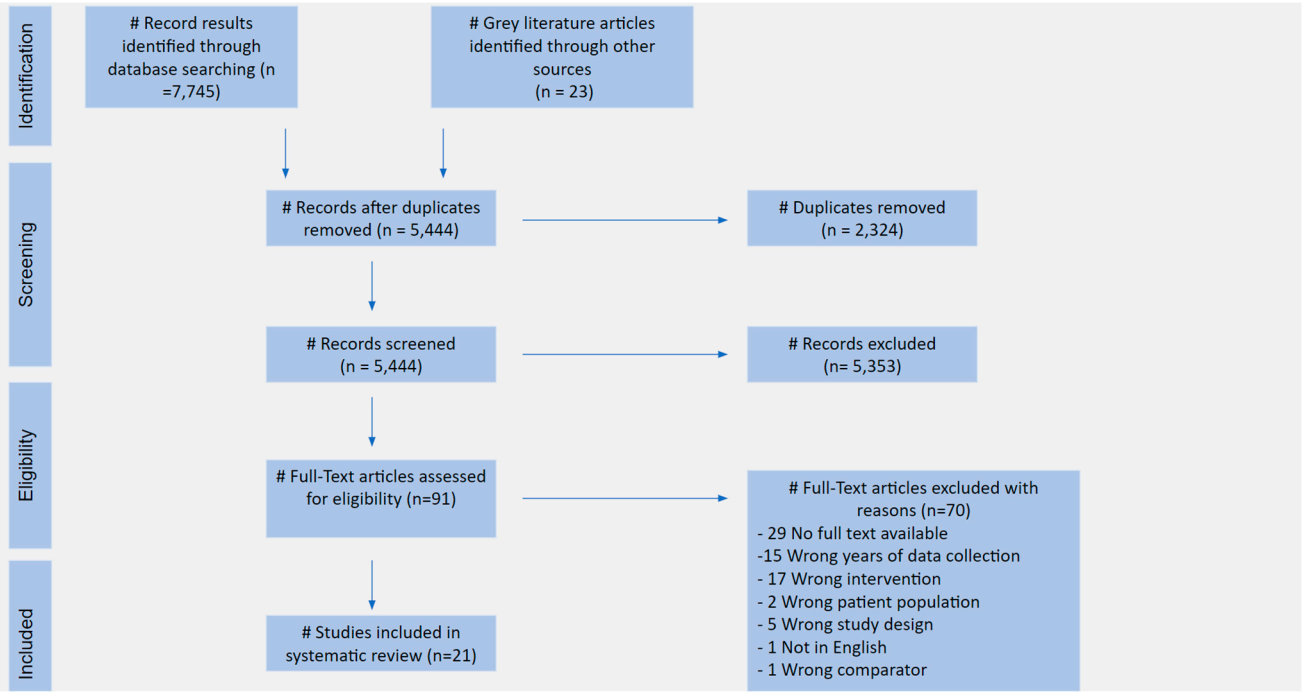

Figure 1. The PRISMA flow diagram of the present systematic review.

3.2. Studies Selected

After the inclusion and exclusion criteria were applied, 21 studies were included in the SLR [28–48]. Overall, 18 CEAs and three CUAs were included. All studies assessed the economic impacts of insulin in the treatment of T2D. Table 2 includes the basic characteristics of each study included.

Table 2. Basic characteristics of each study included in the concept of the present systematic review.

#	First Author	Year of Publication	Setting	Study Type	Comparison
1	Cannon, A.J. [28]	2020	USA	Cost-effectiveness analysis	Insulin degludec/liraglutide versus basal insulin and basal-bolus therapy
2	Cheng, H. [29]	2019	China	Cost-effectiveness analysis	Insulin degludec versus insulin glargine
3	Dempsey, M. [30]	2018	USA	Cost-effectiveness analysis	Insulin degludec/liraglutide versus insulin glargine U100 plus insulin aspart
4	Drummond, R. [31]	2018	UK	Cost-effectiveness analysis	Insulin degludec/liraglutide versus insulin glargine U100 plus insulin aspart
5	Evans, M. [32]	2023	UK	Cost-effectiveness analysis	Insulin aspart versus once-weekly semaglutide

Table 2. *Cont.*

#	First Author	Year of Publication	Setting	Study Type	Comparison
6	Gu, S. [33]	2020	China	Cost-effectiveness analysis	Insulin vs. other agents (10 pharmacologic combination strategies overall)
7	Han, G. [34]	2022	China	Cost–utility analysis	Insulin degludec/liraglutide versus its single components—degludec or liraglutide
8	Hunt, B. [35]	2017	USA	Cost-effectiveness analysis	Insulin degludec/liraglutide versus insulin glargine U100
9	Jiang, Y. [36]	2023	China	Cost-effectiveness analysis	Insulin glargine U100/lixisenatide versus insulin degludec/insulin aspart
10	Kvapil, M. [37]	2017	Czech Republic	Cost-effectiveness analysis	Insulin degludec/liraglutide versus basal insulin intensification strategies
11	Langer, J. [38]	2019	Japan	Cost-effectiveness analysis	Insulin degludec vs. other basal insulins
12	Lau, E. [39]	2019	Hong Kong	Cost-effectiveness analysis	Insulin glargine U100 versus NPH * insulin
13	Luo, Q. [40]	2022	China	Cost-effectiveness analysis	Insulin degludec/insulin aspart versus biphasic insulin aspart 30
14	McCrimmon, R.J. (iGlarLixi vs. basal insulin plus metformin) [41]	2021	UK	Cost-effectiveness analysis	Insulin glargine U100/lixisenatide versus insulin degludec/liraglutide and the free-combination comparators insulin glargine plus dulaglutide and basal insulin plus liraglutide
15	McCrimmon, R.J. (iGlarLixi Versus iDegLira) [42]	2021	UK	Cost-effectiveness analysis	Insulin glargine U100/lixisenatide versus insulin degludec/liraglutide
16	Pöhlmann, J. (ClinicoEcon Outcomes) [43]	2019	Italy	Cost-effectiveness analysis	Insulin degludec/liraglutide versus insulin glargine U100/lixisenatide
17	Pöhlmann, J. (Diabetes Ther.) [44]	2019	Czech Republic	Cost-effectiveness analysis	Insulin degludec/liraglutide versus insulin glargine U100/lixisenatide
18	Pollock, R.F. [45]	2019	Canada	Cost-utility analysis	Insulin glargine versus dulaglutide
19	Pollock, R.F. [46]	2018	UK	Cost-utility analysis	Insulin degludec versus insulin glargine U100
20	Pollock, R.F. (Applied Health Economics and Health Policy) [47]	2019	UK	Cost-effectiveness analysis	Insulin degludec versus insulin glargine U100
21	Raya, P.M. [48]	2019	Spain	Cost-effectiveness	Insulin degludec/liraglutide versus comparator regimens

UK—United Kingdom; USA—United States of America; * NPH—Neutral Protamine Hagedorn.

3.3. Methodology of Selected Studies

Most selected studies included data from clinical trials or pooled analyses and literature reviews to populate the models. Studies #1, #3, #4, #5, #7, #8, #9, #10, #13, #14, #15, #16, #17, #18, #19 and #20 included data from clinical trials and reviews, with some studies including data from local cohort studies. Study #7 used real-world-data (RWD) in addition to clinical trial data. The authors of studies #2, #6, #11, #12 and #21 used RWD. The original authors of all studies used publicly available data and monetary information to construct the economic variables of the models.

3.4. Quality Appraisal

All studies that were selected met the inclusion/exclusion criteria and the BMJ score threshold. Comprehensive quality appraisal results are presented in Table 3 below.

Table 3. Overview of quality appraisal of individual studies based on BMJ health economics checklist and associated scoring.

#	First Author	Score on BMJ * Checklist
1	Cannon, A.J. [28]	34/35
2	Cheng, H. [29]	35/35
3	Dempsey, M. [30]	35/35
4	Drummond, R. [31]	34/35
5	Evans, M. [32]	35/35
6	Gu, S. [33]	34/35
7	Han, G. [34]	35/35
8	Hunt, B. [35]	35/35
9	Jiang, Y. [36]	32/35
10	Kvapil, M. [37]	33/35
11	Langer, J. [38]	35/35
12	Lau, E. [39]	34/35
13	Luo, Q. [40]	35/35
14	McCrimmon, R.J. (iGlarLixi vs. basal insulin plus metformin) [41]	34/35
15	McCrimmon, R.J. (iGlarLixi Versus iDegLira) [42]	34/35
16	Pöhlmann, J. (ClinicoEcon Outcomes) [43]	35/35
17	Pöhlmann, J. (Diabetes Ther.) [44]	34/35
18	Pollock, R.F. (2019) [45]	35/35
19	Pollock, R.F. (2018) [46]	35/35
20	Pollock, R.F. (Applied Health Economics and Health Policy) [47]	35/35
21	Raya, P.M. [48]	34/35

* BMJ—British Medical Journal.

3.5. Evidence Synthesis

3.5.1. CEA Studies

Cheng et al. found that treatment with insulin degludec (IDeg), when compared to insulin glargine (iGlar), was associated with improved Quality-Adjusted Life years (QALYs) (+0.0053) and life expectancy (0.0082 years) in insulin-naive patients with T2D living in China, with an additional total mean lifetime cost of USD 3278 and an Incremental Cost-Effectiveness Ratio (ICER) of USD 613,443 per QALY gained [29]. The authors assert that reduced cumulative incidence of myocardial infarction, stroke and congestive heart failure in the IDeg arm might have been potential reasons for their findings.

Moreover, Langer et al. state improved effectiveness in terms of QALYs (+0.0354), slightly higher annual treatment costs (JPY 9510) and a better value-for-money assessment (JPY 268,811 per QALY gained) for Japanese patients switching from basal insulin to IDeg [38].

Pollock et al., based on evidence from DEVOTE 16, found that treatment with IDeg in UK-based patients was associated with superior cost-effectiveness in contrast to IGlar U100 (ICER GBP 14,956/QALY) [47]. Treatment with IDeg had also slightly superior results pertaining to life expectancy (6.8980 years vs. 6.7825 years) at mean costs of GBP 47,311 (versus GBP 45,582) per patient.

Cannon et al. conducted a short-term CEA in the US, comparing insulin degludec/liraglutide (IDegLira) with basal insulin and basal-bolus therapy, using DUAL V and DUAL VII clinical study data [28]. The rates of reaching double or triple composite outcomes (HbA1c $\leq$ 7.5%, $\leq$8.0%, and $\leq$9.0%) were significantly higher for IDegLira versus IGlar U100 or other basal-bolus regimens for all targets, both in DUAL V and DUAL VII. For each USD 1 spent on IDegLira, the equivalent annual costs per patient to achieve the aforementioned HbA1c targets without hypoglycemia and without weight gain were USD 2.43, USD 2.10 and USD 2.05 for IGlar U100, and USD 6.33, USD 5.80 and USD 6.06, respectively for basal-bolus therapy. A long-term US CEA by Dempsey et al. outlined that IDegLira usage (in comparison to iGlar U100 + insulin aspart) was associated with an increase in discounted life expectancy and discounted quality-adjusted life expectancy (QALE) by 0.02 years and 0.22 QALYs, respectively [30]. The authors argued that these increases were driven primarily by a small reduction in the cumulative incidence of diabetes-related complications and delayed time to their onset. Regarding direct mean medical costs over a patient lifetime, treatment with IDegLira resulted in a USD 3571 cost saving; mostly due to lower acquisition costs as well as lower rates of hypoglycaemia and cardiovascular complications in the IDegLira arm.

Drummond et al. suggested an annual improvement of 0.0512 QALYs for IDegLira; however direct costs were somewhat higher (GBP 303) because of higher acquisition costs in the UK market (GBP 828) [31]. When combining clinical and cost outcomes, an ICER of GBP 5924 per QALY was reported for IDegLira in the treatment of patients with TD2 not reaching glycaemic targets on basal insulin therapy. Hunt et al. also observed IDegLira superiority over iGlar U100 up-titration in terms of annual costs among HbA1c $\leq$ 6.5 without hypoglycaemia (USD 10,608), weight gain (USD 29,215) and their combination (USD 57,351) in US-based patients [35]. Furthermore, in a CEA study in the Czech Republic, treatment with IDegLira was associated with a gain in QALE of 0.31 QALYs, with an additional cost of CZK 107,829 (Czech Koruna) over a patient's lifetime (compared to insulin intensification regimens), which corresponds to an ICER of CZK 345,052 per QALY gained [37]. The authors theorised that the latter was mostly driven by a reduction in the incidence of diabetes-related complications and in the prolongation of symptom onset.

Pöhlmann et al. (ClinicoEcon Outcomes) associated treatment with IDegLira with superior outcomes, when compared to insulin glargine/lixisenatide (iGlarLixi) (gained 0.09 LY and 0.13 QALYs) in Italian patients, as a result of lower cumulative incidence of diabetes-related complications and their delayed onset [43]. Treatment with IDegLira (versus iGlarLixi) yielded an ICER of EUR 7368 per QALY, which fell below the Willingness-To-Pay (WTP) threshold and confirmed its cost-effectiveness. In addition, Pöhlmann et al. (Diabetes Ther.) mentioned an association of IDegLira treatment with superior cost-effectiveness over iGlarLixi in Czech patients [44], a gain in life expectancy of 0.11 years, QALE of 0.14 QALYs (mainly driven by the same diabetes complication reasons) and an ICER of CZK 695,998 (versus iGlarLixi pens containing 33 lg/mL of lixisenatide) and CZK 348,223 (versus 50 lg/mL) per QALY gained, which was below the pre-specified WTP threshold.

Treatment with IDegLira was associated with improved clinical outcomes, i.e., decreased diabetes-related complications and increased QALE, and reduced costs compared with other injectable regimens in a CEA conducted in Spain [48]. When compared to multiple daily insulin injections and basal insulin, ICERs of EUR 3013/QALY and EUR 6890/QALY were reported.

Jiang et al. found that treatment with iGlarLixi (net increase of 0.08 QALYs and 0.07 LE over a patient's lifetime) was dominant over insulin degludec/insulin aspart (IDegAsp) with the projection of an annual medication cost of USD 590.41 to USD 865.03 in Chinese patients [36]. McCrimmon et al. conducted a CEA on a population of UK citizens with TD2, who were suboptimally controlled on basal insulin plus metformin, and demonstrated lower estimated costs with iGlarLixi (GBP 31,295) compared with iGlar plus dulaglutide (Dula) (GBP 38,790), iDegLira (GBP 40,179), and BI plus liraglutide (Lira) (GBP 42,467) [41].

Total QALYs gained were 8.438 with iGlarLixi and iDegLira, 8.439 with iGlar plus Dula, and 8.466 with BI plus Lira; and the net monetary benefit was positive when compared to all other comparators. In another study by the same leading author, conducted on a population of UK citizens with TD2 inadequately controlled by GLP-1 receptor agonists (GLP-1RA) and oral antihyperglycemic therapy, iGlarLixi was reported to be less costly (owing to acquisition costs) compared to iDegLira (GBP 30,011 versus GBP 40,742), whilst at the same time being associated with similar QALYs: 8.437 and 8.422, respectively [42]. The net monetary benefit of iGlarLixi was GBP 11,030.

Luo et al. compared biphasic insulin aspart (BIAsp) 30 and IDegAsp strategy and found an incremental benefit of 0.0001 LYs (12.439 for BIAsp 30 versus 12.438 for IDegAsp), a 0.280 QALYs gain (9.522 versus 9.242) over a 30-year period, and an ICER of Chinese Yuan (CNY) 13.886/QALY for the IDegAsp strategy [40].

Evans et al. conducted a study evaluating the long-term cost-effectiveness of once-weekly semaglutide 1 mg versus insulin aspart in the UK [32]. Despite higher treatment costs (GBP 800) in the semaglutide arm, it was associated with superior cost-effectiveness due to an improvement in QALE of 0.18 QALYs, as a result of a decreased incidence in diabetes complications and delay in disease progress, while also having an ICER of GBP 4457/QALY.

In a comparison between iGlar U100 and Neutral Protamine Hagedorn (NPH) insulin, the former was associated with an incremental gain of 0.217 QALYs and a cost of Hong Kong Dollar (HKD) 21,360, which coincided with an ICER of HKD 98,663/QALY [39].

Gu et al. showed that metformin + insulin (following a second-line treatment with metformin + glinide) had superior cost-effectiveness results in Chinese patients, gaining 14.085 QALYs, among the ten treatment strategies assessed by the authors (extensively described within Gu et al.) [33]. Scenario analyses showed that patients who report adherence on pharmacologic treatments increased their QALYs (0.456~0.653) at an acceptable range of cost increase (ICERs, USD 1450/QALY~USD 12,360/QALY) and in some cases, at decreased costs compared with those not receiving treatment.

3.5.2. CUA Studies

A combination therapy of IDegLira did not demonstrate 'financial superiority' over its monotherapy components (IDeg and Lira) in the treatment of T2D in a CUA conducted in China [34]. No gains were observed in QALYs (11.79, 11.62, and 11.73, respectively), medications costs (USD 20,281.61, USD 3726.76 and USD 11,941.26, respectively), complication costs (USD 25,274.22, USD 25,016.67 and USD 25,204.84, respectively), total costs (USD 45,555.83, USD 28,743.43 and USD 36,660.18, respectively), incremental cost–utility ratio values (USD 99,464.12/QALYs and USD 143,348.26/QALYs, respectively; both surpassed the WTP threshold) nor net monetary benefits (−10,447.67 and −6200.68, respectively).

Both CUA studies positioning iGlar U100 as a 'financial protagonist' were published by Pollock et al. and conducted in Canada and the UK, respectively. Treatment with iGlar U100 was inferior to GLP-1RA agent dulaglutide (when used as a third-line therapy in Canada) in terms of QALE (12.52 vs. 12.90 QALYs) and ICER (CAD 52,580 per QALY gained) [45]. In the second study, treatment with IDeg was superior to iGlar U100 (when compared with basal-bolus regimens in the treatment of patients with T2D in the UK), reporting cost savings of GBP 28.78 per patient (particularly among a population at high risk of the development of heart disease) and a 0.0064 increase in QALYs (1.4778 versus 1.4715, mostly due to lower hypoglycemia risk) [46].

4. Discussion

There are many blood-glucose-lowering treatments with varied clinical outcomes and costs available worldwide. Insulin and GLP-1RA therapies have been continuously developed and approved in order to help patients better manage glycemic control. Generally, newer products such as insulin degludec/DegLira and semaglutide with more positive clinical outcomes were associated with higher acquisition costs but lower healthcare costs

due to mitigated hypoglycemia or other T2D complications during short and long-term CEAs. Specifically, IDeg and DegLira were always found to be more cost-effective therapies than basal-bolus or insulin glargine therapies when hypoglycemic events were considered. The studies where they were not found to be suitable cost-effective alternatives included a UK study where a lower cost generic biosimilar of iGlarLixi was used to calculate the iGlarLixi acquisition cost, which was then compared to branded iDegLira and a study conducted in China where hypoglycemic events were not considered a potential risk factor for subsequent cardiovascular outcomes [36,42]. The latter of these is significant, as all of the studies reporting IDeg and similar insulin mixes to be more effective than insulin glargine variants considered hypoglycemic events, which were key in determining IDeg variants to be more cost-effective. Additionally, a CUA in China found treatment with combination therapy iDegLira to be significantly less cost-effective than either degludec or liraglutide monotherapy despite achieving the highest QALY, due to its high cost in the Chinese market [34].

Cost-effectiveness assessments are important due to the high absolute costs of insulin therapy. Though markets for insulin across the nine countries covered in this review vary in both size and most commonly prescribed insulin analogue, significant healthcare resources are dedicated to procuring insulin for T2D patients.. The average standard unit of insulin (100 units of insulin/mL of fluid) in each of the countries covered in this review cost USD 98.7 in the USA, USD 14.4 in Japan, USD 12 in Canada, USD 10.03 in Italy, USD 9.04 in Spain, USD 8.18 in the Czech Republic and USD 7.52 in the UK. The wide range of insulin prices is due to both reimbursement practices and the types of insulin analogues most commonly prescribed.

New therapies, whether novel compounds or combination therapies, are often associated with high prices that can negatively impact their cost-effectiveness despite clear clinical benefits. In wealthier countries where payer systems have a higher capacity to absorb increased upfront acquisition costs, these products can be attractive, cost-effective alternative treatments compared to established lower-cost alternatives when downstream associated health costs are substantially decreased. The characteristics of countries' health payer systems and their approaches to optimising health can impact criteria used to determine whether interventions are cost effective. Beyond using different criteria to assess the cost-effectiveness of therapeutics, systems may approach allocating scarce resources differently, perhaps opting to prioritise acquisition costs over potential downstream savings. Other factors impacting CEAs and CUAs in different markets are the variance in availability and acquisition costs of therapeutic products and reimbursement for care. Combined, all these factors have the collective effect of creating country-specific scenarios that are not necessarily directly comparable or generalizable. Despite this heterogeneity, assessing the global cost-effectiveness of insulin therapies in the management of T2D allows for the care landscape to be better understood, hopefully leading to better outcomes for all patients with T2D.

The primary strengths of this SLR include the robustness of the study selection process and inclusion of studies across low-, medium- and high-income levels, with a variety of payer systems. Both reviewers assessing all 5444 abstracts sourced from the databases listed in the Methods section allowed for early consensus building and the mitigation of selection bias. Among the 21 studies that met the inclusion/exclusion criteria, 6 were UK-focused, 5 China-focused, 3 USA-focused, 2 Czech Republic-focused, 1 Spain-focused, 1 Japan-focused, 1 Italy-focused, 1 Canada-focused and 1 Hong Kong-focused.

Limitations to this review include the inability to directly compare studies due to different data sources, variables or heterogeneous results, and the majority of the reviewed studies having received industry funding from an organisation manufacturing at least one of the assessed products. Studies used different clinical outcomes, assumptions and models even when using similar methodologies to conduct CEAs or CUAs. The studies focussing on China differed from the rest of the studies reviewed as they did not consider hypoglycemic events caused by insulin when assessing cost-effectiveness; however besides

this, there were not significant regional differences in health economic evaluations of insulin. Lastly, though seven diverse regions were assessed in this SLR, the findings may not be generalizable to other regions due to differences in therapeutic availability, pricing and reimbursement. This review could still be used as a foundation for more directly applicable research in regions not directly addressed. Despite these weaknesses, we are confident that the comprehensive search and selection process, following PRISMA guidelines and using quality assessment tools for each included study, has allowed for a strong review of the literature focused on pharmacoeconomic evaluations of insulin in the management of T2D.

To the best of our knowledge, no SLR including CUAs and CEAs published after 2016 on the use of insulin in the management of T2D has been published recently. In 2015, Zhong et al. published an SLR including CUAs in the management of both types of diabetes, while Saunders et al. conducted an SLR on the cost-effectiveness of intermediate-acting, long-acting, ultralong-acting, and biosimilar insulins in the treatment of T1D [49,50]. In addition, Shafie et al. and Suh et al. performed SLRs on the cost-effectiveness of insulin in the management of both types of diabetes [51,52]. The authors of the latter concluded that insulin detemir is more cost-effective than NPH and as cost-effective as iGlar. Saunders et al., writing about T1D, reported superior cost-effectiveness of long-acting insulin over intermediate-acting insulin. Shafie et al. called for more research to be conducted on the cost-effectiveness of insulin analogues in the treatment of T2D and Zhong et al. asserted that practice needs to be optimised with the use of value-for-money interventions. Hence, we are positive that our work provides an updated insight in the research around insulin and T2D management.

Novel, increasingly expensive therapies based on innovative science are being continuously developed to combat T2D, and as such, it is important for healthcare providers and payers to be able to identify optimal therapies and treatment algorithms for their healthcare settings. Growing understanding of and ability to affect mechanisms of T2D yield new treatment options with new therapeutic outcomes and risks. However, newer therapies are not always necessarily better for patients and health systems, whether looking at therapeutic outcomes, cost, or a combination of both. Novel therapies associated with increased therapeutic benefit are often expensive during their exclusivity period, which can negatively impact their cost-effectiveness. This relationship is not static however, as generic and biosimilar therapies can often offer similar or identical benefits at a lower price point, positively improving the cost-effectiveness of a given therapy. These lower-cost options are not ubiquitous in their availability, meaning that different settings may still generate heterogenous assessments of the most cost-effective T2D interventions. Regardless of setting, healthcare needs are far vaster than the available finite resources, marking the importance of cost–benefit analyses spanning the therapeutic landscape. Reviews such as this can be helpful tools for collating work conducted in a variety of settings to help build understanding of the therapeutic landscape. More research exploring etiologies of T2D and associated therapeutic outcomes linked to existing and novel interventions will help bolster the foundation of knowledge that can better help payers, providers, and patients make more optimal care decisions. Developing more consistent models with these acquired data will allow for more effective cross-market comparisons of cost effectiveness, helping all patients with T2D receive more cost-effective care while mitigating the burden on healthcare systems.

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Appendix A

Table A1. The comprehensive search strategy that was used on Pubmed/Medline, Embase, and Global Health.

Search Strategy	
PubMed	(diabetes) AND (insulin) AND (econom* OR economic evaluation). af
Embase	(diabetes) AND (insulin) AND (econom OR economic evaluation). af
Global Health	(diabetes) AND (insulin) AND (econom* OR economic evaluation). af
Medline	(diabetes) AND (insulin) AND (econom* OR economic evaluation). af
Limitations	
PubMed	2016–2023 The results of the search were filtered only for English papers
Embase	English Language 2016–Current
Global Health	English Language 2016–Current
Medline	2016–Current The results of the search were filtered only for English papers

af—All fields.

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