TINJAUAN STUDI KOMPARATIF MENGENAI ANALISIS MINIMALISASI BIAYA DAN EFEKTIVITAS BIAYA PENGOBATAN DIABETES MELITUS TIPE 2

REVIEW OF COMPARATIVE STUDIES ON THE ANALYSIS THE COST-MINIMIZATION AND COST-EFFECTIVENESS OF TYPE 2 DIABETES MELLITUS TREATMENT

YETMILKA FLORENSIA ARRING
N111 13 518

PROGRAM STUDI FARMASI
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SKRIPSI

Untuk melengkapi tugas-tugas dan memenuhi
syarat-syarat untuk mencapai gelar sarjana

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Pada tanggal, 4 Agustus 2020

SKRIPSI

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Disusun dan diajukan oleh :

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Pada Tanggal, 4 Agustus 2020
Dan dinyatakan telah memenuhi syarat

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Makassar, 4 Agustus 2020

Yang menyatakan,

YETMILKA FLORENSIA ARRING

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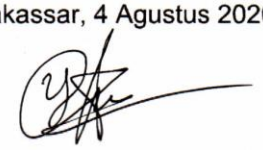

Yetmilka Florensia Arring

ABSTRAK

YETMILKA FLORENSIA ARRING. Tinjauan Studi Komparatif Mengenai Analisis Minimalisasi Biaya dan Efektivitas Biaya Pengobatan Diabetes Melitus Tipe 2. (dibimbing oleh A.Ilham dan Anshar).

Diabetes Melitus merupakan penyakit yang tidak bisa sembuh total, bahkan butuh perawatan lama dan menghabiskan biaya yang tidak sedikit. oleh karena itu efisiensi dan efektivitas penggunaan obat dan biayanya merupakan faktor yang penting diperhatikan. Penelitian ini bertujuan melakukan tinjauan studi komparatif analisis minimalisasi biaya dan analisis efektivitas biaya pada pengobatan Diabetes Melitus Tipe 2, dengan mengkaji beberapa obat antidiabetes. Pencarian menggunakan 4 database yaitu: Google Scholar, PubMed, Proquest, ScienceDirect. Dari beberapa jurnal, dapat diketahui bahwa tiap antidiabetes menghasilkan efektivitas dan biaya yang berbeda-beda. Dengan metode, obat, komparator, nilai *ACER* dan *ICER* serta dari negara yang berbeda-beda. Hasil yang didapatkan dari review yang telah dilakukan bahwa Insulin glargine merupakan obat yang paling efektif biaya dan metformin merupakan obat yang paling minimal biaya.

Kata Kunci : Diabetes melitus tipe 2, efektivitas biaya, *ICER*, minimalisasi biaya, *ACER*

ABSTRACT

YETMILKA FLORENSIA A. Review Of Comparative Studies On The Analysis the Cost-Minimization and Cost-Effectiveness Of Type 2 Diabetes Mellitus Treatment (supervised by A. Ilham and Anshar).

Diabetes Mellitus is a disease that cannot be completely cured, it even takes a long time and costs a lot of money. Therefore the efficiency and effectiveness of drug use and costs are important factor to consider. This study aims to conduct a comparative study of cost minimization analysis and cost effectiveness analysis in the treatment of type 2 diabetes mellitus, by examining several anti-diabetic drugs. A search of 4 electronic database i.e: Google Scholar, PubMed, Proquest, ScienceDirect. From several journals, it can be seen that each anti-diabetic produces different effectiveness and costs. With also different methods, drugs, comparators, ACER and ICER values, and from different countries. The results obtained from review that has been carried out that insulin glargine is the most cost effectiveness drug and metformin is the most cost minimization drug.

Keyword : Type 2 Diabetes Melitus, Cost-Effectiveness, *ICER*, Cost-Minimization, *ACER*

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BAB I

PENDAHULUAN

I.1 Latar Belakang

Diabetes mellitus telah dikategorikan sebagai penyakit global oleh *World Health Organization* (WHO). Data statistik *International Diabetes Federation Atlas* (2013) memperkirakan 382 juta populasi dewasa di seluruh dunia hidup dengan diabetes, angka ini akan terus meningkat hingga mencapai 592 juta pada tahun 2035. Meluasnya epidemi diabetes di seluruh dunia memberikan potensi yang merugikan pada pengembangan system kesehatan dan ekonomi di negara-negara yang sedang berkembang (Kemenkes, 2014).

Diabetes melitus adalah kelompok penyakit metabolik yang ditandai dengan keadaan hiperglikemia dan terjadi karena gangguan sekresi insulin, kerja dari insulin atau kedua-duanya. Hiperglikemia yaitu tingginya kadar glukosa di dalam darah. Hal ini terjadi ketika tubuh memproduksi hormon insulin yang terlalu sedikit atau tubuh tidak mampu menggunakan insulin tersebut dengan baik (American Diabetes Association, 2020).

Diabetes mellitus (DM) didefinisikan sebagai salah satu penyakit atau gangguan metabolism kronis dengan multi etiologi yang ditandai dengan tingginya kadar gula darah disertai dengan gangguan metabolisme karbohidrat, lipid dan protein sebagai akibat insufisiensi

fungsi insulin (DiPiro, dkk, 2009; Kerner, 2014). Insufisiensi insulin dapat disebabkan oleh gangguan atau defisiensi produksi insulin oelh sel-sel beta langerhans kelenjar pankreas, atau disebabkan oleh kurang responsifnya sel-sel tubuh terhdap insulin (Dirjen Binfar Alkes, 2005).

Suatu terapi pengobatan yang baik dan benar akan sangat menguntungkan bagi pasien, baik dari segi kesehatan atau kesembuhan penyakit yang diderita, biaya yang harus dikeluarkan, dan kepatuhan pasien dalam mengkonsumsi obat tersebut terutama lagi bagi pasien yang harus mengkonsumsi obat dalam waktu lama, bahkan seumur hidupnya, seperti penyakit diabetes mellitus, oleh karena itu efisiensi dan efektivitas penggunaan obat dan biayanya merupakan faktor yang penting di perhatikan (Tri Murti, 2006).

Dewasa ini, farmakoekonomi telah tumbuh menjadi salah satu metode yang diperhatikan dalam penyusunan standar-standar pengobatan. Metode ini memungkinkan pengambil kebijakan kesehatan membuat keputusan terkait obat dan juga untuk berbagai intervensi kesehatan lainnya yang memiliki nilai efektivitas sebanding dengan biayanya, terutama dalam prespektif kesehatan masyarakat (Dirjen Binfar & Alkes, 2013).

Oleh karena itu pada penelitian tinjauan studi ini digunakan dua analisis farmakoekonomi, yaitu Analisis Minimalisasi Biaya (AMB) dan Analisis Efektivitas Biaya (AEB) bagi penderita Diabetes Militus tipe II yang dilaporkan dalam beberapa studi sebelumnya. Analisis Efektivitas

Biaya (AEB) adalah analisis yang membenadingkan biaya suatu intervensi dengan bebarapa ukuran non moneter, dimana pengaruhnya terhadap hasil perawatan kesehatan. Sedangkan Analisis Minimalisasi Biaya (AMB) adalah tipe analisis yang membandingkan dua pilihan (opsi, option) intervensi atau lebih yang memberikan hasil (*outcomes)* kesehatan setara untuk mengidenfikasi pilihan yang menawarkan biaya lebih rendah (Dirjen Binfar & Alkes, 2013).

Penelitian tinjauan studi ini dilakukan karena pada saat ini bertepatan terjadi Pandemi Corona Virus (COVID-19), sehingga tidak memungkinkan pengambilan data secara langsung dilakukan di rumah sakit. Penyusunan data diperoleh dari berbagai publikasi literatur resmi yang dilaporkan 10 tahun terakhir sesuai dengan topik penelitian ini. Disamping itu diharapkan hasil penelitian ini dapat menjadi sumber acuan maupun sebagai masukan bagi pihak yang berwenang dalam pengambilan keputusan terkait penentuan kebijakan, khususnya di bidang ekonomi kesehatan.

I.2 Rumusan Masalah

Apakah penilaian efektivitas biaya dan minimalisasi biaya dapat memberikan rekomendasi terapi terbaik serta memperkirakan biaya paling efektif untuk pengobatan Diabetes Melitus tipe 2.

I.3 Tujuan Penelitian

Tujuan penelitian ini adalah untuk melakukan tinjauan studi komparatif tentang analisis minimalisasi biaya dan analisis efektifitas biaya pada pengobatan Diabetes Melitus Tipe 2, dengan mengkaji beberapa obat antidiabetes yang paling *cost effective* dan *cost minimal*, yang digunakan baik secara tunggal maupun kombinasi.

BAB II

TINJAUAN PUSTAKA

II.1 Diabetes Mellitus

II.1.1 Definisi

Diabetes Melitus merupakan gangguan metabolisme yang ditandai dengan hiperglikemia karena kerusakan pada sekresi insulin. Dalam jangka panjang dapat menyebabkan komplikasi yang dapat mempengaruhi mata, ginjal dan saraf, serta meningkatkan resiko penyakit kardiovaskuler *(Canadian Diabetes Association 2013*). Menurut *American Diabetes Association* (2015), Diabetes Melitus merupakan suatu penyakit kronis kompleks yang membutuhkan perawatan medis yang lama atau terus menerus dengan cara mengendalikan kadar gula darah untuk mengurangi resiko multifaktorial.

II.1.2 Patofisiologi dan Etiologi

1. Diabetes Mellitus Tipe 1

DM tipe ini secara umun berkembang di masa lanak-kanak atau dewasa dan merupakan tipe diabetes yang sedikit populasinya, diperkirakan menyumbang kurang dari 5-10% dari keseluruhan populasi yang terkena diabetes. Pada DM Tipe 1 terjadi gangguan produksi insulin karena adanya kerusakan pada sel-sel β pulau Langerhans yang disebabkan oleh reaksi otoimun. Pada pulau Langerhans kelenjar pankreas terdapat beberapa tipe sel yaitu, sel-sel β yang memproduksi

insulin, sel-sel α memproduksi glukagon, dan sel-sel δ memproduksi hormon somatostatin. Namun ada beberapa virus yang dapat menyebabkan DM Tipe 1, yaitu virus Cocksakie, Rubella, CMVirus, Herpes, dan sebagainya. Adapun beberapa tipe otoantibodi yang dihubungkan dengan DM Tipe 1 yaitu, ICCA (*Islet Cell Cytoplasmic Antibodies*), ICSA *(Islet Cell Surface Antibodies*), dan antibodi terhadap GAD (*Glutamic Acid Decarboxylase*). Proses destruksi otoimun dari sel-sel β pulau Langerhens kelenjar pankreas yang mengakibatkan defisiensi sekresi insulin. Defisiensi insulin yang dapat menyebabkan gangguan metabolisme dan fungsi sel-sel α kelenjar pankreas juga menjadi tidak normal pada penderita DM Tipe 1 (*Pharmaceutical Care* untuk Penyakit Diabetes Mellitus, 2005 dan Wells dkk. 2008).

2. Diabtes Mellitus Tipe 2

DM Tipe 2 merupakan tipe diabetes yang pada lebih banyak penderitanya dibandingkan dengan DM Tipe 1 dan diperkirakan jumlah penderita DM Tipe 2 mencapai 90-95% dari kesuluruhan populasi penderita diabets. Umunya DM tipe ini terjadi pada usia <45 tahun, tetapi adanya peningkatan populasi penderita DM Tipe 2 dikalangan remaja dan anak-anak. Penyebab terjadinya DM Tipe 2 merupakan multifaktor yang sepenuhnya belum jelas. Faktor genetik dan pengaruh lingkungan merupakan salah satu faktor yang cukup besar dalam menyebabkan terjadinya DM Tipe 2 yaitu, obesitas, diet tinggi lemak, diet rendah serat, dan kurang beraktivitas atau kurang gerak badan. Pada DM tipe ini

umumnya pada tahap awal dapat dideteksi jumlah insulin yang cukup di dalam darah dan kadar glukosa yang juga tinggi. Patofisiologis pada DM Tipe 2 bukan disebabkan oleh kurangnya sekresi insulin, tetapi adanya resistensi insulin karena sel-sel sasaran insulin tidak mampu merespon insulin secara normal. Resistensi insulin dimanifestasikan oleh peningkatan lipolisis, peningkatan produksi asam lemak bebas, peningkatan produksi glukosa hati, dan penurunan serapan oto rangka glukosa (*Pharmaceutical Care* untuk Penyakit Diabetes Mellitus, 2005).

3. Diabetes Mellitus Gestasional (GDM)

GDM adalah suatu kondisi diabtes atau intoleransi glukosa yang terjadi selama masa kehamilan dan biasanya bersifat sementara atau temporer. Diperkirakan sekitar 4-5% wanita hamil menderita GDM dan umumnya penderita terdeteksi pada trisemester kedua atau setelah trisemester kedua. Terjadinya diabetes pada masa kehamilan dapat pulih dengan sendirinya setelah melahirkan, namun tidak menutup kemungkinan dapat berakibat buruk pada bayi yang dikandung diantara lain, malformasi kongenital, peningkatan berat badan bayi ketika lahir dan meningkatnya risiko mortalitas perinatal. Pada ibu hamil yang pernah menderita GDM akan lebih besar terkena risiko diabetes di masa mendatang, oleh karena itu diperlukan kontrol metabolisme yang ketat untuk mengurangi risiko tersebut (*Pharmaceutical Care* untuk Penyakit Diabetes Mellitus, 2005).

II.1.3 Klasifikasi

Diabetes Melitus bisa diklasifikasikan dalam klasifikasi umum sebagai berikut (ADA, 2015):

1. Diabetes Melitus tipe 1 yang disebabkan oleh kerusakan pada sel beta pankreas dan biasanya termasuk ke dalam defisiensi insulin absolut.
2. Diabetes Melitus tipe 2 yang disebabkan oleh kerusakan progresif pada sekresi hormon insulin sehingga mengakibatkan resistensi insulin.
3. Diabetes Melitus gestasional yang terdiagnosa pada kehamilan trimester kedua atau ketiga dan biasanya setelah melahirkan akan kembali dalam keadaan normal.
4. Diabetes Melitus tipe lain, seperti diabetes neonatal, adanya penyakit eksokrin, atau obat-obatan yang menyebabkan diabetes melitus.

II.1.4 Gejala

Gejala diabetes seringkali muncul tanpa disadari, namun terdapat beberapa gejala yang sering dirasakan oleh penderita diabetes yaitu, poliuria (sering buang air kecil), polidipsia (sering haus), dan polifagia (banyak makan/mudah lapar). Adapun keluhan yang sering muncul diantaranya, penglihatan kabur, koordinasi gerak anggota tubuh terganggu, kesemutan pada tangan atau kaki, timbul gatal-gatal pada kulit yang seringkali sangat mengganggu (pruritus), dan berat badan enurun tanpa sebab yang jelas.

Gejala pada DM Tipe 1 adalah gejala klasik yang umum ditemukan yaitu poliuria, polidipsia, polifagia, penurunan berat badan, cepat merasa

lelah (fatigue), iritabilitas, dan pruritus. Sedangkan gejala pada DM Tipe 2 seringkali muncul tanpa disadari dan penanganan akan dilakukan beberap a tahun kemudian ketika penyakit sudah berkembang dan komplikasi telah terjadi. Umumnya penderita DM Tipe 2 lebih mudah terkena infeksi, sukar sembuh dari luka, daya penglihatan makin buruk, dan umumnya penderita mengalami hipertensi, hiperlipidemia, obesitas, dan juga komplikasi pada pembuluh darah syaraf.

Seseorang yang telah memiliki satu atau lebih faktor risiko diabetes tidak menutup kemungkinan akan menderita diabetes, untuk itu diperlukan kesadaran sejak dini untuk mengetahui dan menangani kondisi diabetes mellitus (*Pharmaceutical Care* untuk Penyakit Diabetes Mellitus, 2005).

Hiperglikemia yang kronik akan berdampak pada kerusakan jangka panjang seperti kegagalan dan disfungsi berbagai organ, seperti mata (retinopati), ginjal (nefropati), saraf (neuropati). Selain itu juga bisa menyebabkan kegagalan organ lain seperti jantung dan pembuluh darah (WHO, 2011; WHO,2012).

II.1.5 Kriteria Diagnosis

Tabel 1. Kriteria Diagnosis Diabetes Melitus (ADA, 2015)

	Glukosa Plasma Puasa	Glikosa Plasma 2 jam setelah makan
Normal	<100 mg/dL	<140 mg/dL
Prediabetes	100 mg/dL – 125 mg/dL	140 mg/dL – 199 mg/dL
Diabetes	>126 mg/dL **	>200 mg/dL

*****Tidak ada pemasukan kalori selama 8 jam sebelum tes dilakukan

Selain kriteria pada table 1 tersebut, untuk mendiagnosis DM tipe 2 juga bisa dilihat dari kadar A1C yaitu ≥ 6,5 %, kadar glukosa plasma 2 jam setelah pemberian Tes Toleransi Glukosa Oral (TTGO) yaitu ≥200 mg/dL serta kadar glukosa plasma secara acak/sewaktu (GDS) yaitu ≥200 mg/dL yang disertai dengan gejala klinis DM.

II.1.6 Penatalaksanaan Terapi

Penatalaksanaan dilakukakan pada diabetes mellitus bertujuan untuk menurunkan morbidibitas serta mortilitas diabetes dengan memiliki dua tujuan spesifik utama, yaitu menjaga agar kadar glukosa plasma berada dalam kisaran normal dan mencegah atau meminimalkan kemungkinan terjadinya komplikasi diabetes. Pada penatalaksanaan diabetes mellitus pada dasarnya terdapat dua terapi pengobatan, yaitu yang pertama pengobatan secara Non Farmakologi dan Pengobatan secara Farmakologi. Pengobatan secara Farmakologi akan dilakukan apabila tidak tercapai tujuan penatalaksaan pengobatan secara Non Farmakologi.

II.1.6.1 Pengobatan Non Farmakologi

Pada terapi ini terdapat beberapa cara untuk menghindari risiko terkena DM, berikut terapi tanpa obat :

1. Pengaturan diet

Pengobatan tersebut merupakan salah satu kunci keberhasilan penatalaksanaan diabetes. Diet yang dianjurkan adalah dengan mengimbangi makanan dengan karbohidrat, lemak, dan protein yang

seimbang sesuai dengan kecukupan gizi (karbohidrat 60-70%, protein 10-15%, dan lemak 20-25%). Dengan adanya berat badan ideal atau penurunan berat badan telah dibuktikan dapat mengurangi resistensi insulin dan memperbaiki respon sel-sel β terhadap stimulus glukosa.

2. Olah Raga

Berolah raga secara teratur juga merupakan salah satu kunci keberhasilan penatalaksanaan DM karena dapat menurunkan dan menjaga kadar gula darah tetap normal. Olah raga ringan apabila dilakukan secara teratur akan sangat besar pengaruhnya bagi kesehatan. Olah raga yang disarankan adalah bersifat CRIPE (Continuous, Rhytmical, Interval, Progressive, Endurance Training), antara lain jalan atau lari pagi, berenang, dan bersepeda. Olah raga aerobik tersebut dapat dilakukan selama 30-40 menit per hari yang di dahului dengan pemanasan 5-10 menit dan diakhiri pendinginan antara 5-10 menit. Olah raga yang dilakukan dapat meningkatkan dan memperbanyak jumlah aktivitas reseptor dalam tubuh serta meningkatkan penggunaan glukosa (Pharmaceutical Care untuk Penyakit Diabetes Mellitus, 2005 dan Wells dkk. 2008).

II.1.6.2 Pengobatan Farmakologi

Seperti dikatakan sebelumnya, bahwa pengobatan ini akan dilakukan apabila pengobatan secara Non Farmakologi tidak tercapai dalam menurunkan kadar gula dalam darah. Pada pengobatan ini

diperlukan langkah pengobatan berupa obat-obatan baik berupa terapi insulin, terapi obat oral hipoglikemik, atau kombinasi keduanya.

1. Terapi Insulin

Terapi insulin merupakan pengobatan yang harus digunakan bai penderita DM Tipe 1, hal ini dikarenakan sel-sel β Langerhans kelenjar pankreas pada penderita rusak sehingga tidak dapat memproduksi insulin. Namun bagi penderita DM Tipe 2 sebagian besar tidak memerlukan terapi insulin kecuali terapi lain yang diberikan tidak dapat mengendalikan kadar gula dalam darah, selain itu DM Gestasional juga membutuhkan terapi insulin. Pada umumnya sekresi insulin dapat dikendalikan oleh tubuh untuk menstabilkan kadar gula dalam darah. Apabila kadar gula dalam darah tinggi, maka sekresi insulin akan meningkat. Tetapi apabila kadar gula dalam darah rendah, maka sekresi insulin dalam darah menurun. Rute pemberian insulin pada umumnya dapat dilakukan melalui subkutan dan intramuskular, namun yang lebih sering digunakan yaitu rute pemberian secara subkutan. Penyerapan insulin paling cepat terjadi di abdomen, lengan, paha bagian atas, dan bokong. Rute pemberian secara intramuskular merupakan rute pemberian yang penyerapannya akan terjadi lebih cepat dan masa kerjanya menjadi lebih singkat (*Pharmaceutical Care* untuk Penyakit Diabetes Mellitus, 2005).

Pada terapi insulin terdapat berbagai jenis sediaan insulin yang berbeda secara mula kerja (onset), masa kerja (duration), peak, dan durasi maksimum. Berikut jenis sediaan insulin dibawah ini :

Tabel 2. Jenis-jenis sediaan insulin

S

Jenis insulin	Onset	Peak (jam)	Durasi (jam)	Durasi maksimum (jam)
Masa kerja cepat				
Aspart	15-30 min	1-2	3-5	5-6
Lispro	15-30 min	1-2	3-4	4-6
Glulisine	15-30 min	1-2	3-4	5-6
Masa kerja singkat				
Regular	30-60 min	2-3	3-6	6-8
Masa kerja sedang				
NPH	2-4 jam	4-6	8-12	14-18
Masa kerja panjang				
Glargine	4-5 jam	-	22-24	24
Detemir	2 jam	6-9	14-24	24

Wells dkk. 2008

Pada DM Tipe 1, kebutuhan insulin rata-rata harian adalah 0,5-0,6 unit/kg, sedangkan untuk DM Tipe 2 kebutuhan insulin yaitu 0,7-2,5 unit/kg (sering diperlukan untuk pasien dengan resistensi insulin yang signifikan).

Jenis insulin masa kerja cepat, merupakan analog yang lebih cepat diserap, memuncak lebih cepat, dan memiliki durasi aksi yang lebih pendek daripada insulin reguler. Pada jenis insulin ini sebaiknya diberikan dalam waktu 10 menit setelah makan (daripada 30 menit sebelumnya), sehingga mendapatkan hasil yang maksimal dalam menurunkan glukosa darah prostprandial dibandingkan insulin reguler pada DM Tipe 1 dan meminimalkan hipoglikemia pasca makan. Pada jenis insulin reguler, memiliki onset aksi yang relatif lambat ketika diberikan secara subkutan

dan membutuhkan waktu injeksi 30 menit sebelum makan untuk mendapatkan hasil optimal dalam mengontrol glukosa postprandial dan untuk mencegah hipoglikemia pasca makan (Wells dkk. 2008).

Menurut Perkumpulan Endokrinologi Indonesia atau PERKENI (2006), penatalaksanaan DM tipe 2 meliputi aspek edukasi seperti memotivasi dan mendampingi pasien untuk mengubah gaya hidup, terapi gizi medis yaitu keteraturan dalam hal jadwal makan, jenis dan jumlah makanan, kemudian melakukan latihan jasmani yaitu sekitar 3-4 kali dalam seminggu dengan durasi kurang lebih 30 menit serta intervensi farmakologis. Intervensi farmakologis ditambahkan jika sasaran glukosa darah belum tercapai dengan pengaturan makan dan latihan jasmani.

2. Obat Hipoglikemik Oral (OHO)

Berdasarkan cara kerjanya, OHO dibagi menjadi empat golongan, yaitu:

2.1 Pemicu sekresi insulin

a. Sulfonilurea

Mekanisme utama sulfonilurea adalah menstimulasi sekresi insulin endogen dengan cara berikatan dengan reseptor sulfonilurea spesifik pada sel beta pankreas. Efikasi dari sulfonilurea yaitu mampu menurunkan kadar A1C sekitar 0,8 %. Obat golongan sulfonilurea dibagi menjadi dua generasi, yaitu generasi pertama seperti glibenklamid, klorpropamid dan tolbutamid, sedangkan generasi kedua adalah glimepirid, gliburid, dan glikazid. Efek samping sulfonilurea adalah hipoglikemia

terutama pada pemberian glibenklamid dan klorpropamid dan lebih besar efek sampingnya dibandingkan dengan sulfonilurea generasi kedua. Efek hipoglikemia juga lebih besar jika obat diberikan pada pasien yang berusia tua dan memiliki gangguan ginjal dan hati (Nathan *et al.,* 2009, 2012; Harper *et al.*, 2013; Audehm *et al.*, 2014).

b. Glinid

Mekanisme glinid sama dengan golongan sulfonilurea yaitu dengan meningkatkan sekresi insulin. Glinid mampu menurunkan nilai A1Csekitar 0,7 %. Contoh obat golongan ini adalah repaglinid dan nateglinid. Repaglinid diketahui lebih efektif dibandingkan nateglinid dalam menurunkan nilai A1C. Efek samping golongan glinid adalah hipoglikemia, namun lebih ringan dari pada sulfonilurea (Nathan *et al.,* 2009, 2012; Harper *et al.*, 2013; Audehm *et al.*, 2014).

c. Penghambat DPP-4 (*dipeptyl peptidase*-4)

Mekanisme golongan ini adalah dengan menghambat enzim DPP-4 sehingga meningkatkan GIP dan GLP-1 endogen dalam sirkulasi darah dan akhirnya akan memperbaiki sekresi insulin. Contoh obat golongan ini adalah sitagliptin dan saxagliptin. Obat tersebut mampu menurunkan A1C sebesar 0,7 %. Efek sampingnya adalah meningkatkan resiko pankreatitis (Nathan *et al,* 2009, 2012; Harper *et al.*, 2013 ; Audehm *et al.*, 2014).

d. Agonis reseptor GLP-1 (*glucagon-like peptide*-1)

Mekamisme utama golongan ini adalah berikatan dengan reseptor GLP-1 sehingga meningkatkan sekresi insulin. Contoh obat golongan ini

adalah exenatid dan liraglutid. Agonis reseptor GLP-1 mampu menurunkan nilai A1C sebesar 1,0 %. Efek samping yang mungkin terjadi adalah kehilangan berat badan, mual, muntah dan pankreatitis (Nathan *et al.,* 2009, 2012; Harper *et al.*, 2013; Audehm *et al.*, 2014).

2.2 Meningkatkan sensitivitas reseptor insulin

a. Tiazolindindion

Mekanisme golongan tiazolindindion adalah meningkatkan sensitivitas reseptor insulin di jaringan dan hati dengan berikatan pada *peroxisome proliferative activated receptor gamma* (PPAR-$_{\gamma}$). Tiazolindindion mampu menurunkan nilai A1C sekitar 0,8 %. Contoh obat golongan ini adalah pioglitazon dan rosiglitazon. Efek samping pioglitazon adalah meningkankan resiko kanker kandung kemih, sedangkan efek samping rosiglitazon adalah meningkatkan resiko infark miokard dan meningkatkan kadar LDL. Efek samping umum lainnya adalah gagal jantung, retensi cairan dan patah tulang (Nathan *et al.,* 2009; Inzucchi, 2012; Harper *et al.*, 2013; Audehm *et al.*, 2014).

2.3 Menghambat glukoneogenesis

a. Biguanid

Mekanisme golongan biguanid adalah mengurangi pembentukan glikkosa hati dan mengaktifkan AMP-kinase. Contoh obat golongan ini adalah metformin. Metformin merupakan obat pilihan pertama untuk DM tipe 2 dan biasanya diresepkan untuk pasien DM tipe 2 yang mengalami obesitas. Metformin mampu menurunkan nilai A1C sekitar 1,0-1,5 %. Efek

samping metformin adalah gangguan gastrointestinal seperti diare dan kram perut, defisiensi vitamin B12dan resiko asidosis laktat. Obat ini dikontraindikasikan pada pasien DM tipe 2 yang mengalami gangguan ginjal dengan nilai GFR <30mL/menit. Selain itu, metformin juga menyebabkan mual sehingga diberikan pada saat makan atau sesudah makan (Nathan *et al.,* 2009; Inzucchi, 2012; Harper *et al.*, 2013).

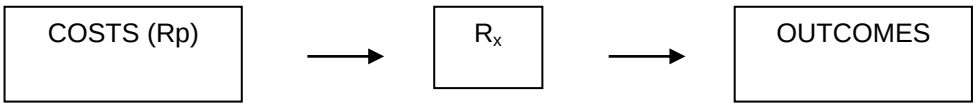
b. Penghambat alfa glukosidase

Mekanisme utama golongan ini adalah menghambat enzim alfa glikosidase dan mengurangi absorpsi karbohidrat di usus halus. Contoh obatnya adalah akarbose. Akarbose mampu menurunkan nilai A1C sebesar 0,6 %. Efek samping yang mungkin terjadi adalah gangguan gastrointestinal seperti diare dan kembung.

II.2 Farmakoekonomi

II.2.1 Definisi

Farmakoekonomi didefinisikan sebagai deskripsi dan analisis biaya terapi obat untuk sistem perawatan kesehatan masyarakat. Ilmu farmakoekonomi adalah ilmu mengidentifikasi, mengukur, serta membandingkan biaya dan manfaat dari produk dan layanan farmasi. Dengan adanya ilmu farmakoekonomi dapat membantu dokter maupun pembuat keputusan lain untuk mengevaluasi dan membandingkan total biaya pilihan perawatan dan hasil yang terkait dengan opsi tersebut. Berikut gambar penjelasan farmakoekonomi :



Gambar 1. Bagan singkat analisis Farmakoekonomi (Rascati., 2009)

Costs atau biaya yang digunakan untuk mendapatkan dan menggunakan produk atau layanan farmasi, sedangkan sisi kanan merupakan hasil atau manfaat yang didapatkan terkait kesehatan yang dihasilkan oleh produk atau layanan farmasi. Produk atau layanan obat yang dinilai atau diukur, yang dilambangkan dengan R_x. Apabila *Costs* diukur tanpa memperhatikan *Outcomes*, maka hal tersebut adalah analisis biaya. Namun, jika hanya *Outcomes* diukur tanpa memperhatikan *Costs*, maka hal tersebut adalah studi klinis atau hasil bukan analisis ekonomi. Oleh karena itu, dibutuhkan *Costs* dan *Outcomes* untuk menjadi analisis farmakoekonomi sejati yang harus dipertimbangkan dan dibandingkan (Rascati., 2009).

Farmakoekonomi terbagi atas dua bagian utama yaitu, *Cost Analysis* dan *Cost Outcome Analysis*. *Cost Analysis* hanya mempertimbangkan dari biaya pelayanan kesehatan berupa jasa tanpa memperhatikan *outcome* / hasil yang harus dibayar oleh penanggung pasien sedangkan *Cost Outcome Analysis* merupakan perbandingan biaya dari pelayanan kesehatan dan hasil tindakan perawatan (Wertheimer, A. dkk, 2012).

Method of analysis	Cost measure	Outcome measure
Cost analysis		
Cost of care	Currency	N/A
Cost-outcomes analysis		
Cost-effectiveness	Currency	Natural units, e.g. life-years saved
Cost-utility	Currency	Quality-adjusted life years or other utility
Cost-benefit	Currency	Currency
Cost-minimization	Currency	Natural units or utilities

Gambar 2. Metodologi dan Analisis Farmakoekonomi **(Weirtheimer, A., Pradelli, L, 2012)**

II.2.2 Prespektif Penilaiaan

Perspektif penilaian merupakan hal penting dalam kajian farmakoekonomi, karena perspektif yang dipilih menentukan komponen biaya yang harus disertakan. Seperti yang telah disampaikan, penilaian dalam kajian ini dapat dilakukan dari tiga prespektif yang berbeda, yaitu:

1. Perspektif masyarakat (*societal*).

Sebagai contoh Kajian Farmakoekonomi yang mengambil perspektif masyarakat luas adalah penghitungan biaya intervensi kesehatan, seperti program penurunan konsumsi rokok, untuk memperkirakan potensi peningkatan produktivitas ekonomi (PDB, produk domestik bruto) atau penghematan biaya pelayanan kesehatan secara nasional dari intervensi kesehatan tersebut.

2. Perspektif kelembagaan (institutional).

Contoh kajian Farmakoekonomi yang terkait kelembagaan antara lain penghitungan efektivitas-biaya pengobatan untuk penyusunan

formularium rumah sakit. Contoh lain, di tingkat pusat, penghitunganAEB untuk penyusunan DOEN dan formularium nasional.

3. Perspektif individu (individual perspective).

Salah satu contoh kajian farmakoekonomi dari perspektif individu adalah penghitungan biaya perawatan kesehatan untuk mencapai kualitas hidup tertentu sehingga pasien dapat menilai suatu intervensi kesehatan cukup bernilai atau tidak dibanding kebutuhan lainnya (termasuk hiburan).

Tabel 3. Jenis Biaya Menurut Perspektif

Komponen biaya	Prespektif			
	Masyarakat	Pasien	Penyedia yankes	Pembayar
Biaya Langsung Medis				
Biaya pelayanan kesehatan	+	+	+	+
Biaya pelayanan kesehatan lainnya	+	±	-	±
Biaya *cost sharing patient*	-	+	-	-
Biaya Langsung Non Medis				
Biaya transportasi	+	±	-	±
Biaya pelayanan informal (tambahan)	+	-	-	-
Biaya tidak langsung				
Biaya hilangnya produktivitas	+	+	-	-

II.2.3 Biaya

Dalam kajian farmakoekonomi, biaya selalu menjadi pertimbangan penting karena adanya keterbatasan sumberdaya, terutama dana. Dalam kajian yang terkait dengan ilmu ekonomi, biaya (atau biaya peluang,

opportunity cost) didefinisikan sebagai nilai dari peluang yang hilang sebagai akibat dari pengunaan semberdaya dalam sebuah kegiatan. Patut dicatat bahwa biaya tidak selalu melibatkan pertukaran uang. Dalam pandangan pada ahli farmakoekonomi, biaya kesehatan melingkupi lebih dari sekadar biaya pelayanan kesehatan, tetapi termasuk pula, misalnya, biaya pelayanan lain dan biaya yang diperlukan oleh pasien sendiri. Dalam proses produksi atau pemberian pelayanan kesehatan, biaya dapat dibedakan menjadi sebagai berikut:

1. Biaya rerata dan biaya marjinal

Biaya rerata merupakan biaya hasil per unit yang diperoleh, sedangkan biaya marjinal adalah perubahan biaya atas penambahan atau pengurangan hasil unit yang diperoleh (Bootman, dkk., 2005). Contoh biaya rerata, yaitu biaya akomodasi. Sedangkan biaya makan, pengobatan, jasa dokter, dan perawat merupakan biaya marjinal yang tidak mengalami perubahan biaya (DirJen Binfar dan Alkes, 2013)

2. Biaya tetap dan biaya variabel

Biaya tetap merupakan biaya yang jumlahnya tidak dapat berubah seiring dengan perubahan kuantitas atau layanan yang diberikan dalam jangka pendek (≤ 1tahun), misalnya gaji karyawan (pasien) dan depresiasi aset. Biaya variabel, merupakan biaya yang dapat berubah seiring adanya perubahan hasil yang diperoleh, misalnya komisi penjualan dan biaya penjualan obat (Bootman, dkk., 2005).

3. Biaya tambahan (*ancillary cost*)

Merupakan biaya atas pemberian tambahan pelayanan pada suatu prosedur medis, misalnya skring sinar-X, anatesi, dan laboratorium (Berger, dkk., 2003).

4. Biaya total

Biaya tersebut merupakan biaya keseluruhan yang harus dikeluarkan untuk memproduksi berbagai pelayanan kesehatan (DirJen Binfar dan Alkes, 2013).

Adapun biaya perawatan kesehatan yang bukan hanya terdiri dari biaya obat ditambah dengan biaya langsung lain. Selain biaya langsung adapun biaya tidak langsung yang harus ditanggung antara lain, biaya transportasi, dan hilangnya produktivitas. Adanya deperesi dan rasa sakit yang juga merupakan biaya yang harus dihitung dan sangat sulit dikonversikan ke unit moneter. Secara umum, biaya berdasarkan perawatan kesehatan dibagi menjadi beberap bagian, yaitu :

1. Biaya langsung

Biaya langsung merupakan biaya yang terkait lasung dengan perawatan kesehatan, yaitu biaya obat, biaya kunjungan dokter, biaya jasa perawat, penggunaan fasilitas rumah sakit, uji labiratorium, biaya pelayan informal, dan biaya kesehatan lainnya biaya (DirJen Binfar dan Alkes, 2013).

2. Biaya tidak langsung

Biaya ini merupakan sejumlah biaya yang terkait langsung dengan hilangnya produktivitas akibat adanya suatu penyakit yang diderita, antara lain biaya hilangnya produktivitas, dan biaya pendamping pasien selama perawatan (Bootman, dkk., 2005).

3. Biaya nirwujud (*intangible cost*)

Merupakan biaya yang sulit diukur kedalam unit moneter, tetapi seringkali terlihat dalam pengukuran kualitas hidup pasien, misalnya rasa sakit dan rasa cemas yang dialami pasien dan/atau keluarganya (DirJen Binfar dan Alkes, 2013).

4. Biaya terhindarkan (*averted cost, avoided cost*)

Biaya tersebut merupakan potensi pengeluaran yang dapat dihindarkan karena penggunaan suatu pengobatan kesehatan (Berger, dkk., 2003).

Selain itu, masih ada beberapa istilah biaya lainnya yang bersifat teknis terkait dengan perawatan kesehatan. Beberapa biaya yang juga sering diperhitungkan dalam telaah ekonomi kesehatan teersebut antara lain:

1. Biaya perolehan (*acqusition cost*)

Biaya perolehan adalah biaya atas pembelian obat, alat kesehatan dan/atau intervensi kesehatan, baik bagi individu pasien maupun institusi (Berger et al., 2003).

2. Biaya yang diperkenankan (*allowable cost*)

Biaya yang diperkenankan adalah biaya atas pemberian pelayanan atau teknologi kesehatan yang masih dapat ditanggung oleh penyelenggara jaminan kesehatan atau pemerintah pasien maupun institusi (Berger et al., 2003).

3. Biaya pengeluaran sendiri (*out-of-pocket cost*)

Biaya pengeluaran sendiri adalah porsi biaya yang harus diabayar oleh individu pasien dengan uangnya sendiri. Sebagai contoh, iuran biaya peserta asuransi kesehatan (Berger et al., 2003).

4. Biaya peluang (*opportunity cost*)

Biaya peluang adalah biaya yang timbul akibat pengabilan suatu pilihan yang mengorbankan pilihan lainnya. Bila seorang pasien memutuskan untuk membeli obat A, dia akan terkena baiya peluang karena tak dapat menggunakan uangnya unutk hal terbaik lainnya, termasuk pendidikan, hiburan, dan sebagainya (Bootman et al., 2005).

Identifikasi jenis-jenis biaya dapat berkembang sesuai kasus yang dikaji. Jenis biaya yang disertakan dalam farmakoekonomi tergantung pada pertanyaan yang ingin dijawab. Terkait dengan hal ini, secara umum hasil kajian farmakoekonomi dapat diukur dari tiga perspektif: masyarakat, kelembagaan (pengambilan kebijakan, penyedia pelayanan kesehatan, asuransi kesehatan), dan individu (misalnya pasien).

II.2.4 Metode Analisis

Pada analisis farmakoekonomi, dikenal empat metode yang sering digunakan. Empat metode analisis ini tidak hanya mempertimbangkan keamanan, efektivitas, dan kualitas obat, tetapi juga mempertimbangkan aspek ekonominya. Aspek ekonomi atau unit moneter telah menjadi prinsip dasar dalam ilmu farmakoekonomi, hasil yang ditemukan diharapkan mampu memberikan masukan untuk memilih dan menetapkan penggunaan yang paling efisien dari sumber daya kesehatan yang terbatas jumlahnya. Berikut akan dirincikan pada tabel 11.

Tabel 4. Metode Analisis dalam ilmu Farmakoekonomi

Metode analisis	Karakteristik analisis
Analisis minimalisasi biaya (AmiB)	Efek dua intervensi sama (atau setara), valuasi/ biaya dalam rupiah
Analisis efektivitas biaya (AEB)	Efek dari satu intervensi lebih tinggi, hasil pengobatan diukur dalam unit alamiah/indikator kesehatan, valuasi/biaya dalam rupiah
Analisis utilitas-biaya (AUB)	Efek dari suatu intervensi lebih tinggi, hasil pengobatan dalam *quality-adjust* life years (*QALY*), valuasi/ biaya dalam rupiah
Analisis manfaat biaya (AMB)	Efek dari satu intervensi lebih tinggi, hasil pengobatan dinyatakan dalam rupiah

Sumber : *Newby and Hill, 2003*.

II.2.4.1 Analisis Minimalisasi Biaya

Pada metode AMiB ini merupakan metode yang paling sederhana, hanya dapat digunakan untuk membandingkan dua atau lebih intervensi kesehatan, termasuk pemberian obat yang memberikan hasil yang sama, serupa, atau setara. Karena hasil pengobatan dari intervensi adalah sama, maka yang perlu dibandingkan hanya biaya. Namun jarang

ditemukan dua terapi yang setara atau dibuktikan kesetaraannya, maka penggunaan AMiB agak terbatas.

II..2.4.2 Analisis Efektivitas Biaya

Analisis AEB banyak digunakan dalam penelitian atau analisis farmakoekonomi dan merupakan analisis yang cukup sederhana untuk membandingkan dua atau lebih intervensi kesehatan yang memberikan efek berbeda (Rascati., 2009). Dengan menggunakan AEB yang mengukur biaya sekaligus hasil, maka pengambil kebijakan dapat memilih alternatif terbaik diantara sejumlah intervensi kesehatan dan termasuk obat yang digunakan.

Pada metode AEB dilakukan perhitungan rasio biaya rerata dan rasio inkremental efektifitas biaya (RIEB = *incremental cost-effectiveness ratio/ ICER*). Apabila RIEB dapat diketahi jumlah besar biaya tambahan untuk setiap perubahan satu init efektivitas biaya dan juga membantu pengambil keputusan untuk memilih alternatif mana yang memberikan efektivitas biaya terbaik.

Hasil CEA dipresentasikan dalam bentuk rasio, yaitu *Average Cost Effectiveness Ratio* (ACER) atau dalam *Incremental Cost Effectiveness Ratio (*ICER). ACER menggambarkan total biaya dari program atau intervensi dibagi denga iuran klinik, yang dapat dihitung dengan rumus sebagai berikut (DiPiro *et al* 2005).

$$\text{ACER} = \frac{Biaya\ Perawatan\ Kesehatan(\$)}{Efektivitas\ (\$)}$$

ICER digunakan untuk mendeterminasikan biaya tambahan dan pertambahan efektivitas dari suatu terapi dibandingka terapi yang paling baik, yang dapat dihitung dengan rumus sebagai berikut (DiPiro *et al* 2005).

$$\text{ICER} = \frac{Biaya\ A(\$) - Biaya\ B(\$)}{Efek\ A(\$) - Efek\ B(\$)}$$

Tabel 5. Penggolongan Alternatif berdasarkan Efektivitas Biaya

Efektivitas biaya	Biaya lebih rendah	Biaya sama	Biaya lebih tinggi
Efektivitas lebih rendah	A (Perlu perhitungan RIEB)	B (Didominasi)	C (Didominasi)
Efektivitas sama	D (Didominasi)	E (Seimbang)	F (Didominasi)
Efektivitas lebih tinggi	G (Didominasi)	H (Didominasi)	I (Perlu perhitungan RIEB)

Sumber : Rascati., 2009

Pada posisi dominasi (kolom G, D, dan H), jika suatu intervensi kesehatan menawarkan efektivitas lebih tinggi dengan biaya lebih rendah (kolom G) atau efektivitas lebih tinggi dengan biaya sama (kolom H), dan efektivitas yang sama dengan biaya lebih rendah (kolom D), maka akan terpilih sehingga tidak perlu dilakukan AEB.

Pada posisi dominasi (kolom C, B, dan F), jika efektivitas lebih rendah dengan biaya lebih tinggi, dan efektivitas lebih rendah dengan biaya sama (kolom B), atau efektivitas sama dengan biaya lebih tinggi (kolom F), maka tidak perlu dilakukan perhitungan AEB.

Pada posisi seimbang (kolom E), adalah sebuah intervensi yang menawarkan efektivitas yang sama dan biaya yang sama masih dapat

untuk dipilih apabila lebih mudah diperoleh dan/atau cara pemakaiannya lebih memungkinkan kepatuhan oleh pasien. Oleh karena itu, dalam posisi ini ada faktor lain yang perlu dipertimbangkan, antara lain : kebijakan, ketersediaan, aksebilitas, dll.

Posisi yang memerlukan pertimbangan efektivitas biaya (kolom A dan I), jika suatu interventi kesehatan menawarkan efektivitas yang lebih rendah dengan biaya yang lebih rendah pula (kolom A) atau menawarkan efektivitas yang lebih tinggi dengan biaya yang lebih tinggi, maka diperlukan perhitungan RIEB.

II.2.4.3 Analisis Utilitas Biaya

Pada penggunaan metode AUB hampis sama dengan metode AEB tetapi hasilnya dinyatakan dengan utilitas yang berhubungan dengan peningkatan kualitas atau perubahan kualitas akibat intervensi kesehatan yang dilakukan. Adapun beberapa istilah yang digunakan dalam metode AUB, yaitu :

1.Utilitas (*utility)*, adalah unit utilitas yang digunakan dalam metode farmakoekonomi yang biasanya “jumlah tahun yang disesuaikan” (JKTD) atau *quality-adjusted life years* (*QALY*)

2. Kualitas hidup (*quality of life, QOL*), merupakan kualitas hidup yang diukur dengan menggunakan dua pendekatan yaitu pendekatan kuatitas (*duration of life*) dan pendekatan kualitas (*quality of life*) (Bootman, et al., 2005)

3.QALY (*quality-adjusted life years*) atau JKTD merupakan suatu hasil dari suatu intervensi yang diharapkan dengan berhubungan erat dengan kualitas hidup.

II.2.4.4 Analisis Manfaat Biaya

Metode analisis ini menghendaki adanya perhitungan secara ekonomi terhadap manfaat yang diperoleh dari suatu intervensi pengobatan, karenanya antara biaya dan manfaat dari suatu pengobatan harus ekuivalen dalam ukuran nilai uang. Analisis ini sangat bermanfaat pada kondisi antara manfaat dan biaya mudah dikonversi ke dalam bentuk rupiah. Pengukuran dapat dilakukan dengan menghitung jumlah episode penyakit yang dapat dicegah, kemudian dibandingkan dengan biaya kalau program kesehatan dilakukan. Makin tinggi ratio *benefit* : *cost*, maka program makin menguntungkan. Metode ini juga digunakan untuk meneliti pengobatan tunggal. Jika rationya lebih dari satu, maka pengobatan dianggap bermanfaat karena ini berarti manfaatnya lebih besar dari biayanya. CBA merupakan analisis yang paling komprehensif dan sulit untuk dilakukan. Berbeda dengan CEA yang menggunakan efek terapeutik sebagai outcome atau CUA yang menggunakan kualitas hidup, maka CBA menggunakan nilai uang dalam mengukur benefit, Namun kekurangan dari metode ini yaitu hal-hal yang termasuk dalam manfaat (benefit) tidak dapat dihitung dalam bentuk angka (Dirjen Binfar & Alkes, 2013).

BAB III

METODE PENELITIAN

III.1 Rancangan Penelitian

Penelitian ini merupakan studi komparatif dengan mengkaji jurnal penelitian terkait analisis minimalisasi biaya dan efektivitas biaya pada pasien Diabetes Melitus tipe II.

III.2 Subjek Penelitian

Subjek penelitian ini adalah jurnal penelitian internasional maupun nasional yang berkaitan dengan analisis minimalisasi biaya dan efektivitas biaya pada pasien Diabetes Melitus tipe II mengikuti pedoman PRISMA dalam melakukan tinjauan. Pangkalan data yang digunakan yaitu: PubMed, Proquest, dan ScienceDirect. Artikel jurnal di dapatkan sesuai dengan kata kunci ("*Cost Effectiveness*" AND "*Cost Minimalization*" AND "ACER" AND "*type II Diabetic Mellitus*" AND "ICER"). Sebanyak 16 jurnal yang didapat. Hasil pencarian ditinjau dan disaring didapatkan 56 jurnal. Pembuatan tabulasi sesuai dengan mengkaji metode, data, hasil, dan kesimpulan membantu dalam menyeleksi jurnal. Jurnal akan ditinjau kembali dan akan diskrining jika terdapat jurnal yang tidak relevan. Sebanyak 25 jurnal yang memenuhi syarat. Selanjutnya diperoleh 9 jurnal setelah dieksklusi dan memenuhi syarat akhir untuk dimasukkan kedalam pembahasan.Sampel dan populasi yang digunakan harus sesuai dengan kriteria inklusi, yaitu :

1.Jurnal internasional yang berkaitan dengan analisis minimalisasi biaya dan efektivitas biaya pada pasien Diabetes Melitus tipe II.

2.Jurnal nasional yang berkaitan dengan analisis minimalisasi biaya dan efektivitas biaya pada pasien Diabetes Melitus tipe II.

3.Jurnal yang dipublikasikan selama 10 tahun terakhir antara tahun 2010-2020.

4.Jurnal yang memiliki metode, data, hasil, dan kesimpulan yang jelas.

5.jurnal yang membahas data nilai *Average Cost Effectiveness Ratio* (ACER) *dan Incremental Cost Effectiveness Ratio* (ICER) dari obat antidiabetes baik tunggal maupun kombinasi.

Adapun kriteria eksklusi yang digunakan dalam pengambilan sampel pada penelitian ini, yaitu :

1.Jurnal internasional yang tidak sesuai topik penelitian.

2.Jurnal nasional yang tidak sesuai topik penelitian.

3.Jurnal yang diterbitkan di bawah tahun 2010

4.Jurnal yang tidak memiliki kelengkapan metode, data, hasil dan kesimpulan yang jelas.

5.Jurnal yang tidak membahas data nilai *Average Cost Effectiveness Ratio* (ACER) *dan Incremental Cost Effectiveness Ratio* (ICER) dari obat antidiabetes baik tunggal maupun kombinasi**.**

III.3 Tahap Penelitian

1. Pengumpulan jurnal penelitian yang berkaitan dengan analisis minimalisasi biaya dan efektivitas biaya pada pasien Diabetes Melitus tipe II dari sumber internet.
2. Melakukan skrining jurnal dengan memperhatikan kelengkapan metode, data, hasil dan kesimpulan yang jelas berdasarkan pedoman *PRISMA checklist.*
3. Merangkum jurnal berdasarkan metode, data, hasil dan kesimpulan setiap jurnal.
4. Melakukan tabulasi data akhir
5. Menganalisis data dengan membandingkan setiap jurnal penelitian dan pengaruhnya terhadap nilai *Average Cost Effectiveness Ratio* (ACER) *dan Incremental Cost Effectiveness Ratio* (ICER).
6. Penarikan kesimpulan akhir.

III.4 Analisis Data

Analisis data menggunakan analisis deskriptif yaitu merangkum kumpulan data dan disajikan dalam bentuk tabel. Tahapan analisis data, yaitu:

III.4.1 Penyajian Data

Penyajian data dalam bentuk sebuah tabel yang berisikan jurnal, tujuan jurnal, jenis obat, metode, populasi dan sampel, data dan hasil, serta kesimpulan.

III.4.2 Pembahasan

Membahas setiap data tabulasi yang dihasilkan dan membandingkan data yang diperoleh

III.4.3 Penarikan Kesimpulan

Kesimpulan akhir dilakukan dengan cara mengambil kesimpulan dari analisis data yang diperoleh.

BAB IV

HASIL DAN PEMBAHASAN

IV. 1 Hasil Analisis Data

Pada penelitian ini, diperoleh 169 jurnal penelitian yang telah di identifikasi, dan didapatkan 9 artikel jurnal penelitian yang memenuhi kriteria inklusi. Dari 9 artikel jurnal yang telah diinklusi, terdapat metode pengumpulan data yang berbeda dimana dua jurnal menggunakan metode studi farmakoekonomi bersamaan dengan uji klinik yaitu: CORE Diabetes Model (1), QuintilesMS Health CORE Diabetes (1). Tiga jurnal menggunakan metode studi farmakoekonomi dengan modeling yaitu : IQVIA CORE Diabetes Model (2), Markov Model (1). Tiga jurnal menggunakan metode studi farmakoekonomi dengan metode deskriptif.

Tabel.6 Karakteristik studi seleksi Kategori obat Kombinasi

Studi	Negara	Time horizon	Metode/Model	Obat/ Program	Komparator	Nilai (Rp) obat/ program	Nilai (Rp) Komparator	CE
Kwon et al (2018)	Amerika serikat	25 Tahun	Markov Model	Metformin + DPP-4	Metformin + Sulfonilurea	ICER (164.487.818)	ICER (269.588.440)	CE
Wahyuni et al (2012)	Indonesia	3 bulan	Deskriptif	Insulin aspart + Metformin	Insulin detemir+ Metformin	ACER (794.628)	ACER (822.955)	CE
Putra et al (2017)	Indonesia	3 bulan	Deskriptif	Insulin glargine + Metformin	Insulin aspart + Insulin glargine	ACER (431.997)	ACER (1.336.566)	CE

Ningrum et al (2019)	Indonesia	4 bulan	Deskriptif	Sulfonilurea + biguanid	Sulfonilurea + α glikosidase	ACER (427.499)	ACER (883.199)	CE

Ket. Tabel: CE (*Cost Effective*)

Penelitian yang dilakukan oleh Kwon et al (2018) di Amerika serikat membandingkan antara obat DPP-4 dengan sulfonilurea dan sebagai tambahan metformin dengan jangka waktu 25 tahun. Dari hasil penelitian didapatkan kombinasi DPP-4 dan metformin meningkatkan nilai ICER lebih efektif dibandingkan dengan kombinasi sulfonilurea dan metformin. Penelitian ini menggunakan metode *Markov Model*. Di Indonesia pun juga dilakukan penelitian oleh Wahyuni et al (2012) dimana obat yang digunakan yaitu insulin aspartat dan insulin detemir yang masing-masing ditambahkan dengan metformin. Dengan metode deskriptif dengan jangka waktu 3 bulan. Dari hasil kombinasi tersebut didapatkan bahwa kombinasi insulin aspartat dan metformin memiliki nilai ACER yang lebih efektif dibandingkan dengan kombinasi insulin detemir dan metformin.

Penelitian kombinasi Insulin glargine dan metformin yang dibandingkan dengan insulin aspartat juga dilakukan oleh Putra et al (2017) dimana kombinasi Insulin glargine dan metformin memiliki nilai ACER yang efektif Rp 431.997. Dengan metode deskriptif dan 3 bulan penelitian. Ningrum et al (2019) dari Indonesia juga melakukan penelitian dimana selama 4 bulan penelitian tersebut dengan metode deskriptif obat yang digunakan yaitu kombinasi sulfonilurea dan biguanid yang dibandingkan dengan sulfonilurea dan α glikosidase. Hasil yang didapat

dari penelitian tersebut yaitu kombinasi sulfonilurea dan biguanid yang memiliki nilai ACER Rp 427.499,00 yang lebih efektif dibandingkan dengan kombinasi sulfonilurea dan α glikosidase.

Dari hasil yang tertera diatas dapat disimpulkan bahwa untuk kombinasi obat oral yang *cost effective* adalah metformin dan DPP-4. Sedangkan untuk kombinasi insulin dan obat oral yang *cost effective* adalah insulin glargine dan metformin.

Tabel.7 Karakteristik studi seleksi Kategori obat Tunggal Efektif

Studi	Negara	Time horizon	Metode/ Model	Obat/ Program	Kompara tor	Nilai (Rp)	CE
Pèrez et al (2015)	Spanyol	13 bulan	Core Diabetes Model	1.8 mg Liraglutide	Sitagliptin	ICER (888.812.980)	CE
Roze et al (2018)	Finland	6 bulan	IQVIA CORE Diabetes Model	Insulin infusion	Insulin Multiple Daily Injection	ICER (825.312.051)	CE
Kvapil et al (2017)	Czech Republik	3 bulan	Quintiles MS Health CORE Diabetes	IdegLira	Insuln intensification regiments	ICER (417.076.440)	CE
Salem et al (2019)	Hongkong	6 bulan	IQVIA CORE Diabetes Model	Insulin Glargine	NPH Insulin	ICER (177.279.652)	CE

Ket. Tabel: CE (*Cost Effective*)

Di negara Spanyol Pèrez et al (2015) juga dilakukan penelitian dengan membandingkan 1,8 mg liraglutide dengan sitagliptin dengan menggunakan metode CDM (*CORE Diabetes Model*) dengan jangka waktu penelitian selama 13 bulan. Dari penelitian tersebut didapatkan hasil bahwa 1,8 mg liraglutide memiliki nilai ICER yaitu EUR 52,450 atau setara dengan Rp 888.812.980 yang lebih efektif dibandingkan dengan sitagliptin. Dengan menggunakan metode IQVIA CORE *Diabetes Model*, Roze et al (2018) dari Finland juga melakukan penelitian selama 6 bulan dimana penelitian ini membandingkan *insulin infusion* dengan *insulin multiple daily injection*. Dimana *insulin infusion* dengan nilai ICER Rp 825.312.051 lebih efektif dibandingkan dengan dengan *insulin multiple daily injection*.

Di Republik Czech Kvapil et al (2017) juga melakukan penelitian dimana dengan membandingkan Ideglira dengan *Insulin intensification regiments*. Dimana Ideglira memiliki nilai ICER EUR 47,834 atau setara dengan Rp 417.076.440 dimana nilai ini lebih efektif dibandingkan dengan *Insulin intensification regiments*. Pada penelitian ini Kvapil menggunakan metode QuintilesMS *Health CORE Diabetes* dengan jangka waktu penelitian selama 3 bulan. Salem et al (2019) dari negara Hongkong juga melakukan penelitian selama 6 bulan. Dimana pada penelitian ini insulin glargine di bandingkan dengan NPH insulin. Dengan hasil nilai ICER HKD 98,663 atau setara dengan Rp 177.279.652 insulin glargine memiliki nilai

paling efektif dibandingkan dengan NPH insulin. Penelitian ini menggunakan metode IQVIA CORE *Diabetes Model*.

Dari hasil yang tertera diatas dapat disimpulkan bahwa untuk obat oral tunggal yang paling *cost effectiv* adalah 1,8 mg Liraglutide. Sedangkan untuk insulin tunggal yang paling *cost effective* adalah insulin glargine.

Tabel.8 Karakteristik studi seleksi Kategori obat Tunggal Minimal

Studi	Negara	Time horizon	Metode/ Model	Obat/ Program	Komparator	Nilai (Rp) obat/ program	Nilai (Rp) Komparator	CM
Gu et al (2015)	China	1 tahun	Conducted on the assumption	Metformin	Acarbose	3.162.980	5.358.290	CM

Ket. Tabel: CM (*Cost Minimization*)

Di China Gu et al (2015) melakukan penelitian dengan metode *conducted on the assumption* dengan jangka waktu 1 tahun. Dimana Gu membandingkan Metformin dengan Acarbose dengan harapan untuk mencari obat mana yang paling minimalisasi. Dan hasil yang didapatkan bahwa Metformin paling *cost-minimization* dibandingkan dengan Acarbose. Dari hasil yang tertera diatas dapat disimpulkan bahwa untuk obat oral yang paling *cost minimization* adalah Metformin.

Dari 9 jurnal penelitian tersebut metode yang paling banyak dibandingkan yaitu metode deskriptif dan IQVIA CORE *diabetes Model*. Penggunaan metode secara modeling telah banyak dilakukan salah satunya metode *Markov Model.* Pada jurnal yang menggunakan metode modeling markov model biasanya memiliki jangka waktu yang lama untuk mendapatkan hasil yang diinginkan. Dari jurnal tersebut juga ada yang hanya membandingkan obat tunggal dan ada juga yang mengkombinasikannya. Paling banyak yang ditemui yaitu kombinasi insulin denga obat antidiabetik oral.

BAB V

PENUTUP

V.1 Kesimpulan

Berdasarkan pembahasan hasil penelitian di atas, dapat ditarik kesimpulan sebagai berikut :

Hasil yang didapatkan dari review yang telah dilakukan bahwa Insulin glargine merupakan obat yang paling efektif biaya dan metformin merupakan obat yang paling minimal biaya.

V.2 Saran

1. Perlu dilakukan lebih banyak lagi penelitian analisis efektivitas biaya dan minimalisasi biaya pada antidiabetik oral, insulin maupun kombinasi sehingga akan lebih banyak hasil penelitian tersebut.
2. Diharapkan review dapat dilakukan tidak hanya di benua Amerika dan Eropa saja namun di Indonesia juga perlu diperbanyak review agar dapat membantu penelitian lain.

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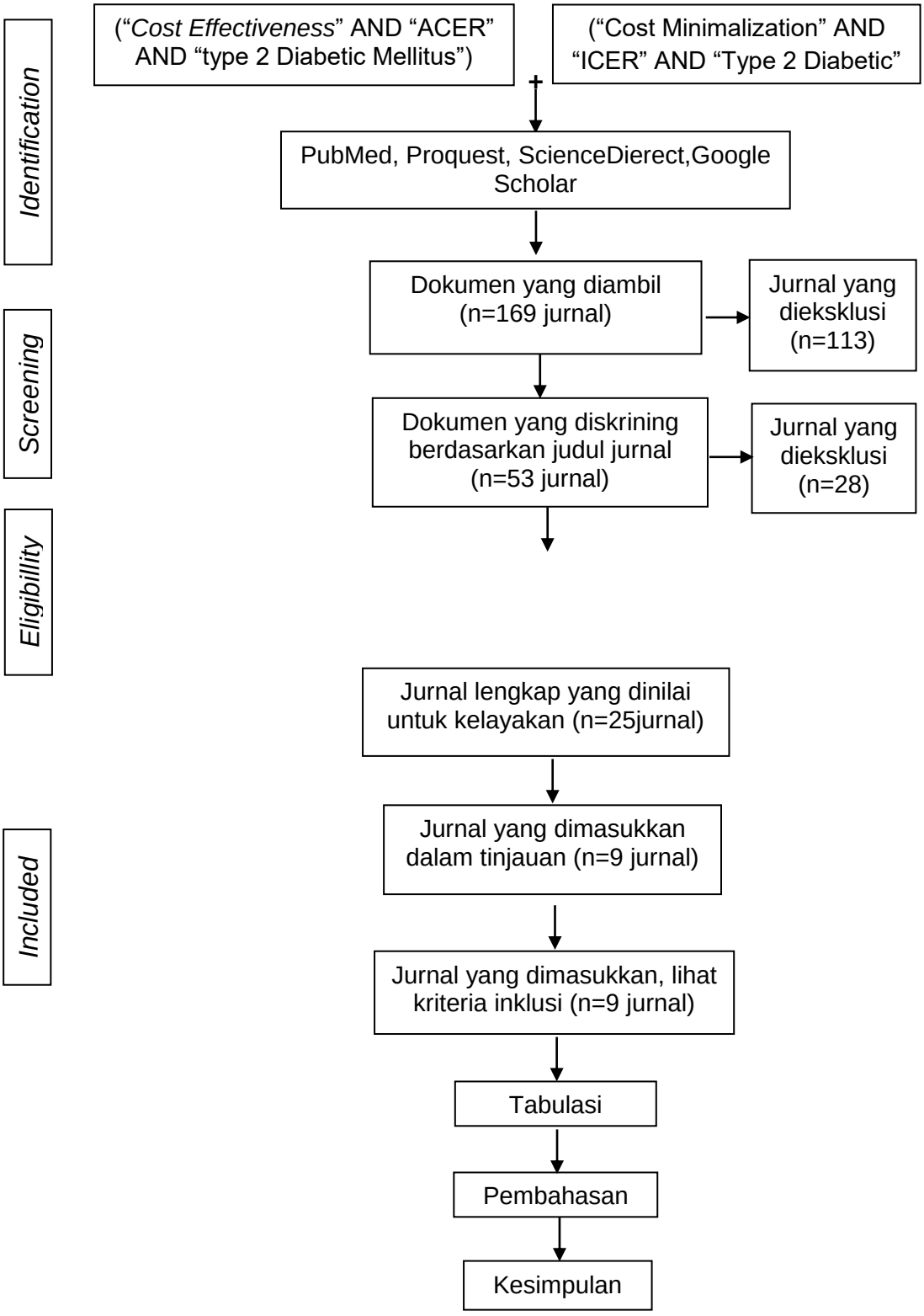
LAMPIRAN I

SKEMA KERJA



LAMPIRAN II

JURNAL

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ORIGINAL RESEARCH

Cost-Effectiveness of IDegLira Versus Insulin Intensification Regimens for the Treatment of Adults with Type 2 Diabetes in the Czech Republic

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ABSTRACT

Introduction: The aim of this study was to evaluate the long-term cost-effectiveness of the insulin degludec/liraglutide combination (IDegLira) versus basal insulin intensification strategies for patients with type 2 diabetes mellitus (T2DM) not optimally controlled on basal insulin in the Czech Republic.

Methods: Cost-effectiveness was evaluated using the QuintilesIMS Health CORE Diabetes model, an interactive internet-based model that simulates clinical outcomes and costs for cohorts of patients with diabetes. The analysis was conducted from the perspective of the Czech Republic public payer. Sensitivity analyses were conducted to explore the sensitivity of the model to plausible variations in key parameters.

Results: The use of IDegLira was associated with an improvement in the quality-adjusted life expectancy of 0.31 quality-adjusted life-years (QALYs), at an additional cost of Czech Koruna (CZK) 107,829 over a patient's lifetime compared with basal–bolus therapy, generating an incremental cost-effectiveness ratio (ICER) of CZK 345,052 per QALY gained. In a scenario analysis, IDegLira was associated with an ICER of CZK 693,763 per QALY gained compared to basal insulin + glucagon-like peptide-1 receptor agonist (GLP-1 RA). The ICERs are below the generally accepted willingness-to-pay threshold (CZK 1,100,000/QALY gained at the time of this analysis).

Conclusions: Results from this evaluation suggest that IDegLira is a cost-effective treatment option compared with basal–bolus therapy and basal insulin + GLP-1 RA for patients with T2DM in the Czech Republic whose diabetes is not optimally controlled with basal insulin.

Funding: Novo Nordisk.

Keywords: Cost-effectiveness; Fixed-ratio combination therapy; IDegLira; QALY; Type 2 diabetes

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INTRODUCTION

Diabetes is a chronic metabolic disorder characterized by elevated levels of blood glucose (hyperglycemia). The disease is associated with considerable morbidity and mortality [1] and represents one of the largest challenges to health worldwide. According to the Institute of Health Information and Statistics of the Czech Republic (UZIS), there were 862,882 people with diagnosed diabetes in the Czech Republic in 2015 (excluding those with impaired glucose tolerance) [2], of whom 91.4% had type 2 diabetes mellitus (T2DM), 6.5% had type 1 diabetes mellitus (T1DM), and the remainder had secondary diabetes [2].

T2DM is characterized by insulin resistance (decreased tissue response to insulin) and a progressive loss of β-cell function, ultimately resulting in insulin deficiency [3]. T2DM is more common in obese adults over 40 years of age, although it is becoming more common in children and adolescents due to increased obesity rates in these groups [4].

The long-term complications of diabetes, which are a consequence of prolonged hyperglycemia, include retinopathy, nephropathy, neuropathy, and cardiovascular disease [1]. A study of patient records of people with T2DM ($n = 495$) in the Czech Republic found that 44.2 and 49.3% of patients had at least one macrovascular complication and at least one microvascular complication, respectively, and that 82.8% of all patients were being treated with anti-hypertensive medications [5]. In 2015 there were 29,000 diabetes-related deaths (2.7 deaths per 1000 population) in the Czech Republic [2].

The treatment of diabetes and its associated complications imposes an immense economic burden on national healthcare systems. In the Czech Republic the mean diabetes-related expenditure per patient with diabetes was estimated to be around EUR 1445.16[1] in 2015 [6].

The clinical goal in the treatment of diabetes is to achieve good glycemic control with minimal hypoglycemia or other adverse effects of treatment, such as weight gain. International guidance recommends a glycated hemoglobin (HbA_{1c}) target of $< 7\%$ (53.0 mmol/mol) [7]. T2DM is a progressive disease [8], and treatment is intensified over time. Most patients with T2DM will eventually require insulin to maintain target HbA_{1c} levels, and many patients will need to intensify their insulin regimen as the disease continues to progress [7]. Guidance in the Czech Republic for the treatment of T2DM is in line with American Diabetes Association (ADA) and European guidance [7, 9]. Common strategies for intensification of insulin therapy are (1) to titrate the basal insulin further, (2) to add bolus insulin, (3) to switch to premix insulin, or (4) to add a glucagon-like peptide-1 (GLP-1) receptor agonist (RA) to the insulin therapeutic regimen. In the Czech Republic guidance, therapy with a fixed combination of GLP-1 receptor agonist and basal insulin and with GLP-1 RA and basal insulin are both recommended [10].

Despite clear guidelines and the availability of many different treatment options, glycemic control remains suboptimal in a substantial number of patients [11, 12]. In a European study, the overall proportion of patients with T2DM not achieving good glycemic control was 37%, rising to 64% when only patients receiving insulin/injectables were considered [13]. An expert survey by IMS Health Technology Solutions Czech Republic s.r.o. found that 53% of patients on basal insulin in the Czech Republic do not have adequate glycemic control [$HbA_{1c} \geq 60$ mmol/mol (7.6%)]. Barriers to intensification of insulin therapy and good glycemic control in these patients include hypoglycemia, weight gain, and complex treatment regimens [14–18].

IDegLira is a once-daily, fixed-ratio combination of the long-acting basal insulin analog (insulin degludec; IDeg) and the GLP-1 RA (liraglutide) administered in a single pen injection device. It was developed to take advantage of the combined effects of IDeg and liraglutide on glycemic control through their complementary mechanisms of action. IDegLira is indicated for the treatment of adults with T2DM to improve glycemic control in combination with oral glucose-lowering medicinal products when these alone or combined with a GLP-1 RA or basal insulin do not provide adequate glycemic control [19]. A suggested place in the T2DM treatment pathway for IDegLira is when these patients are uncontrolled on basal insulin and require treatment intensification.

Two phase 3 DUAL™ (Dual Action of Liraglutide and Insulin Degludec in Type 2 Diabetes) trials provide the core efficacy and safety evidence for IDegLira in patients with T2DM uncontrolled on basal insulin. The DUAL II trial (NCT 01392573; IDegLira vs. IDeg) found that at equivalent insulin doses IDegLira was superior to IDeg in terms of lowering HbA_{1c} and was significantly more favorable in terms of changes in body weight (weight loss with IDegLira vs. no weight change with IDeg) [20]. The results also confirmed that hypoglycemia was numerically lower with IDegLira versus IDeg [20]. The DUAL V trial [NCT 01952145; IDegLira vs. up-titration of insulin glargine U100 (IGlar U100; Lantus®)], which enrolled patients with T2DM uncontrolled on IGlar U100 at trial entry, found that IDegLira was superior to IGlar U100 in terms of lowering HbA_{1c}, change in body weight (weight loss with IDegLira vs. weight gain with IGlar U100), and hypoglycemia [21]. Despite a superior reduction in HbA_{1c} the rate of confirmed hypoglycemia was 57% lower with IDegLira [21].

At the time of data analysis (February 2016) there were no head-to-head clinical trials of IDegLira versus other treatment options for intensification of basal insulin therapy. However, an indirect statistical comparison (pooled multivariable analysis) was conducted to establish an estimate of the treatment effects of IDegLira versus basal–bolus insulin therapy and liraglutide added to basal insulin in patients with T2DM uncontrolled on basal insulin [22]. The pooled analysis showed that IDegLira was associated with a significantly greater decrease in HbA_{1c} versus both basal–bolus therapy and GLP-1 RA added to basal insulin, with lower hypoglycemia rates and a greater reduction in weight versus basal–bolus therapy [22].

In the current environment of cost containment, decision-making based on both clinical and economic evidence is paramount for optimum resource use and service delivery for patients with T2DM. Cost-effectiveness analyses are increasingly used to inform pharmaceutical reimbursement and/or pricing decisions in many countries. Such analyses help decision-makers determine whether the health benefits associated with adopting the novel treatment are worth the cost, compared with existing therapies. The objective of the study reported here was to evaluate the long-term cost-effectiveness of IDegLira versus basal–bolus insulin therapy, as an alternative insulin intensification strategy, in adult patients with type 2 diabetes not optimally controlled on basal insulin in the Czech Republic. The cost-effectiveness of IDegLira versus GLP-1 RA added to basal insulin was investigated in a scenario analysis.

[1] Converted from USD using currency converter http://www.xe.com/currencyconverter, January 2017.

METHODS

Type of Economic Analysis

A cost-effectiveness analysis was conducted to estimate the difference in cost between IDegLira and a comparator, divided by the difference in health effects. A generally accepted effectiveness measure used in cost-effectiveness analyses is the quality-adjusted life-year (QALY). A QALY is an overall measure of health as a combination of the duration of life and the health-related quality of life [23]. The outcome measure is termed an incremental cost-effectiveness ratio (ICER):

$$\text{ICER} = \frac{\text{Cost}_{\text{IDegLira}} - \text{Cost}_{\text{comparator}}}{\text{Effect}_{\text{IDegLira}} - \text{Effect}_{\text{comparator}}}$$

Therefore, the cost-effectiveness (the ICER) was expressed as the cost/QALY gained. An intervention is considered to be cost-effective if the ICER falls below a defined willingness-to-pay (WTP) threshold. In the Czech Republic there is no official guidance on the WTP threshold, but the SÚKL[2] (State Institute for Drug Control) applies a "generally accepted threshold" based on threefold the gross domestic product per capita in all administrative proceedings [24]. At the time of

[2] Státní ústav pro kontrolu léčiv.

this analysis this was 1,100,000 CZK/QALY gained.

Choice of Comparators

In the Czech Republic the most relevant comparator for IDegLira was considered to be basal–bolus therapy, such as, for example, the addition of insulin aspart to insulin glargine three times daily (IGlar + 3 × IAsp). During the administrative reimbursement procedure for IDegLira, SÚKL confirmed that basal–bolus therapy was the only appropriate comparator treatment. The combination of basal insulin and GLP-1 RA could not be considered as it is not reimbursed in the Czech Republic [25]. Therefore, IDegLira versus basal–bolus therapy formed the base case analysis, which was conducted in February 2016. However, as the combination of basal insulin and GLP-1 RA has been included in the recent guidance in the Czech Republic, we investigated this treatment option in an alternative scenario analysis. This analysis was requested by the General Insurance Company of Czech Republic (a healthcare payer) during negotiations that followed the positive Evaluation Report from the SÚKL, and it was conducted in May 2016. The Evaluation Report was issued by SÚKL before the Final Decision to guarantee the participants the right to comment and raise possible objections and provide counter-arguments, thereby ensuring the transparency and fairness of the administrative proceeding during which price and reimbursement levels and conditions are set. In this process, all administrative proceedings are led by the SÚKL, and the Marketing Authorization Holder and insurance companies (healthcare payers) are participants only. The process is completed with the issue of the Final Decision by SÚKL which describes the assessment and the main reasons for the price and reimbursement decisions.

As there were no head-to-head studies comparing IDegLira with basal–bolus therapy and the combination of basal insulin and GLP-1 RA at the time of evaluation, data to inform the analysis were taken from the expanded pooled analysis [22], which includes data from patients receiving IGlar U100 + 3 × IAsp or IDeg + 3 × IAsp in the basal–bolus arm ($n = 210$).

Model Overview

The long-term cost-effectiveness of IDegLira versus relevant comparators was assessed using the QuintilesIMS Health CORE Diabetes model (referred to as the IMS CORE Diabetes model elsewhere in text) and effectiveness data from the expanded pooled analysis. The analysis follows standard methodology as prescribed by the IMS CORE Diabetes model and previously published economic evaluations of IDegLira [26, 27].

The IMS CORE Diabetes model is an internet-based, interactive computer model developed to determine the long-term health outcomes and economic consequences of implementing interventions in the treatment of diabetes [28, 29]. The model allows extrapolation of results from short-term trials to long-term outcomes, and it considers diabetes therapy, oral hypoglycemic medications, screening and treatment strategies for microvascular complications, treatment strategies for end-stage complications, and multifactorial interventions. The following long-term outcomes are evaluated in the model: life expectancy, quality-adjusted life expectancy, cumulative incidence of diabetes-related complications, time to onset of diabetes-related complications, and direct medical costs.

The IMS CORE Diabetes model simulates the complications of diabetes (angina, myocardial infarction, congestive heart failure, stroke, peripheral vascular disease, diabetic retinopathy, macular edema, cataract, hypoglycemia, ketoacidosis, lactic acidosis, nephropathy and end-stage renal disease, neuropathy, foot ulcer, and amputation). It takes data from a number of different sources to perform patient level simulations (Fig. 1). Baseline cohort characteristics are used to define a simulated patient, and treatment effects based on the trial data are applied. Other diabetes management strategies are also included, since these affect the risk of complications. The simulated patient then

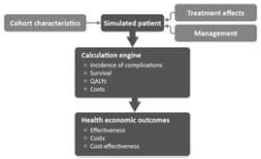

Fig. 1 Performing simulations with the QuintilesIMS Health CORE Diabetes model. QALY Quality-adjusted life year

enters the model, in which clinical events are projected over patient lifetimes. Based on these clinical events and their impact on costs and quality of life, health economic outcomes are projected.

Time Horizon and Treatment Duration

The base case analysis used a lifetime (50-year) time horizon to capture all relevant long-term complications and associated costs in order to assess their impact on life expectancy and quality-adjusted life expectancy. The impact of shortening the time horizon was explored in sensitivity analyses. The model takes into account mortality as a result of diabetes-related complications and background mortality based on Czech Republic-specific life tables [30]. Therefore, while a 50-year time horizon was used, patients were not assumed to live for 50 years. All patients had died after 50 years of the modeling analysis.

Patients receiving IDegLira were assumed to receive the treatment for the first 5 years of the analysis. After 5 years, treatment was intensified to basal–bolus insulin therapy with once-daily IGlar U100 + 3 × IAsp. This assumption recognizes that intensification to basal–bolus therapy will be required for patients to maintain glycemic control over the long term. Patients in the basal–bolus therapy arm were assumed to remain on this therapy for the duration of their lifetime.

Discounting

Clinical and cost outcomes were discounted symmetrically at 3% per annum, which is in line with health economic guidance for the Czech Republic [31].

Clinical Data

A simulated cohort of patients was defined, with baseline risk factors based on the baseline characteristics of patients randomized to receive IDegLira in the DUAL II study (Table 1). The proportion of patients using tobacco products was based on the DUAL II trial data, but the number of cigarettes smoked per day was assumed to be the same as that calculated for the general Czech Republic population and was based on country-specific data [32]. Similarly, mean weekly alcohol consumption was taken from Czech Republic-specific data for the general population [32].

Treatment effects applied in the first year of the analysis (Table 2) were based on data from the expanded pooled analysis [22].

After the first year of the analysis, systolic blood pressure and serum lipids were assumed to follow the natural progression algorithms built into the CORE Diabetes Model, based on the 30-year UK Prospective Diabetes Study (UKPDS 82) or Framingham data (as described by Palmer et al. [29]). Benefits in terms of HbA_{1c} and body mass index (BMI) were assumed to persist for the 5 years that patients received IDegLira and to be abolished upon treatment switching. Hypoglycemia rates following treatment intensification were based on the basal–bolus arm, with non-severe and severe hypoglycemic event rates of 794.63 and 2.85 events per 100 patient-years, respectively, applied.

Costs and Resource Use

Costs were estimated from the Czech Republic public payer perspective. Direct costs captured included pharmacy costs, costs associated with diabetes-related complications, and

Table 1 Baseline cohort characteristics

Demographics and risk factors	Phase 3 DUAL™ II trial cohort (patients receiving IDegLira)
Start age (years)	56.8 (8.9)
Duration of diabetes (years)	10.3 (6.0)
Percentage male	56.3%
HbA_{1c} (%)	8.7 (0.7)
SBP (mmHg)	132.4 (14.8)
Total cholesterol (mg/dL)	182.0 (45.5)
HDL cholesterol (mg/dL)	43.4 (11.0)
LDL cholesterol (mg/dL)	101.9 (37.1)
Triglycerides (mg/dL)	196.8 (148.0)
BMI (kg/m^2)	33.6 (5.7)
Percentage smokers (%)	16.1
Cigarettes per day[a]	14.44
Alcohol consumption (fl oz/week)[b]	5.01

Values in table are presented as the mean with the standard deviation (SD) in parenthesis

BMI Body mass index, *HbA_{1c}* glycated hemoglobin, *HDL* high-density lipoprotein, *IDegLira* fixed-ratio combination of the insulin analog degludec (IDeg) and the glucagon-like peptide-1 (GLP-1) receptor agonist (GLP-1 RA) liraglutide, *LDL* low-density lipoprotein, *SBP* systolic blood pressure, *SD* standard deviation

[a] Source: Sovinova H and Csemy L: The use of tobacco and alcohol in the Czech Republic 2012 [32]

[b] Derived from [32]

concomitant patient management costs. All costs were expressed in 2016 CZK.[3]

Treatment costs were calculated based on the adjusted doses in the expanded pooled analysis from which clinical data on the treatment effects were also taken [22]. One needle was assumed for each injection. Patients were assumed to be receiving metformin in addition to the study medication. Following treatment intensification to basal–bolus therapy, treatment costs were the same in both arms (matched to IGlar U100 + 3 × IAsp). Patients receiving IDegLira were assumed to use one self-monitored blood glucose (SMBG) test per day (comprised of one SMBG test strip and one lancet), and patients receiving IGlar U100 + 3 × IAsp were assumed to use four SMBG tests per day (alternative assumptions around SMBG use were evaluated in sensitivity analyses). The total annual per-patient cost (including drugs, needles, and SMBG testing) was CZK 68,684.14 for IDegLira versus CZK 43,731.35 for IGlar U100 + 3 × IAsp (based on current prices in February 2016 when the analysis was conducted).

Resource use relating to patient management was assumed to be the same as that for the general population with T2DM in the Czech Republic in all treatment arms. Patient management costs captured in the analysis included concomitant medications (aspirin, statins, and angiotensin-converting enzyme inhibitors), screening for renal disease, retinopathy and diabetic foot complications, and post-complication management (such as intensive insulin treatment after myocardial infarction). The cost of treating diabetes-related complications in the

[3] For context 27 CZK was approximately equivalent to 1 EUR at the time of analysis (http://www.xe.com/currencyconverter).

Table 2 Treatment effects applied in patients previously uncontrolled on basal insulin (IDegLira vs. basal–bolus therapy)

Parameter	IDegLira	Basal–bolus therapy
HbA_{1c} (%)	− 1.66 (0.96)	− 1.33* (0.96)
SBP (mmHg)	− 6.86 (13.20)	− 0.93* (13.20)
Total cholesterol (mg/dL)	− 10.13 (30.28)	+ 1.50* (30.28)
HDL cholesterol (mg/dL)	+ 0.52 (6.79)	+ 0.79 (6.79)
LDL cholesterol (mg/dL)	− 6.85 (23.83)	+ 0.08* (23.83)
Triglycerides (mg/dL)	− 25.74 (103.71)	+ 3.82* (103.71)
BMI (kg/m^2)	− 1.04 (1.34)	+ 1.38* (1.34)
Severe hypoglycemia event rate (events/100 PYE)	0.84	2.85
Non-severe hypoglycemia event rate (events/100 PYE)	125.05*	794.63*

Source: Electronic Supplementary Material appendix of extended pooled analysis by Freemantle et al. [22]
Values in table are presented as the mean with the SD in parenthesis
PYE Patient years of exposure
* Statistically significant difference

year of the event and the annual follow-up costs (applied in each year of the simulation subsequent to the first event) were consistent with previous cost-effectiveness analyses in the Czech Republic [see Electronic Supplementary Material (ESM) Appendix for all patient management costs].

Estimation of Quality-Adjusted Life Expectancy

Utilities and disutilities (i.e., measures of the impact on quality of life) associated with complications of diabetes were obtained from published sources [29, 33–36]. Quality-adjusted life expectancy was assessed using the additive "CORE Default Method", which involves taking the lowest health state score associated with existing complications and adding event utilities for any events that occur in that year to create annual health state utility scores for each simulated patient [29].

Sensitivity Analyses

The extrapolation of clinical results by modeling the long-term consequences is associated with uncertainty. Therefore, sensitivity analyses were performed on key parameters in the model to assess the robustness of the base case findings. The following sensitivity analyses were conducted:

- Time Horizon: The influence of time horizon on the outcomes projected by the model was investigated by running analyses over 10 and 20 years. It should be noted that a time horizon of 50 years was required for all modeled patients to have died, and therefore shorter time horizons do not capture all complications and costs.
- Discount Rate: To examine the effect of discounting on cost-effectiveness outcomes, simulations were performed with (symmetric) discount rates of 0 and 5%.
- Key Drivers of Clinical Benefit: Five simulations were run to assess the key drivers of clinical benefit associated with IDegLira. In the IDegLira arm, changes in HbA_{1c}, systolic blood pressure, serum lipids, BMI, and hypoglycemia were set to the value in the IGlar + 3 × IAsp arm in turn. This allowed the contribution of individual clinical effects to long-term health economic outcomes to be assessed.
- Statistically Significant Differences Only: Only the treatment effects that were significantly different between the IDegLira and IGlar + 3 × IAsp arms were applied.
- HbA_{1c} Progression: Two alternative approaches to HbA_{1c} progression were explored. In the first, the UKPDS HbA_{1c} progression equation was applied in both arms of the simulation. HbA_{1c} increases over time in both arms of the analysis, with the HbA_{1c} benefit in the IDegLira arm gradually reduced. In the second approach, no HbA_{1c} changes were applied following the treatment effects applied in the first year of the analysis. This attempts to capture the legacy effect, where an early improvement in HbA_{1c} has a benefit in the later years of life, even if the HbA_{1c} difference is abolished.
- Upper and Lower Limit of HbA_{1c} Change: Simulations were run with the upper and lower 95% confidence interval of the modeled HbA_{1c} change applied in the IDegLira arm. All other parameters in the IDegLira and IGlar + 3 × IAsp arm remained unchanged.
- BMI Progression: The base case analysis assumed that the BMI benefit associated with IDegLira was abolished upon treatment switching, and an alternative to this assumption was explored in a sensitivity analysis, where the difference between the IDegLira and IGlar + 3 × IAsp was maintained for the duration of the analysis.
- Treatment Switching Patterns: To investigate the effect of the timing of treatment switching on cost-effectiveness, simulations were performed, with the year of treatment switch to basal–bolus therapy in the IDegLira arm brought forward to the end of year 3, pushed back to the end of year 7, and no treatment switching. In the IGlar + 3 × IAsp arm no treatment switching was assumed to occur, and therefore changes were only applied in the IDegLira arm.
- Application of Alternative Insulin Costs: A scenario was conducted with the price of NPH insulin (intermediate–acting insulin) applied in the IGlar + 3 × IAsp arm. Conservatively, all other parameters were as per the base case analysis.
- Alternative dosing in the Comparator Arm: Alternative dosing was evaluated in two scenarios. In the first, the defined daily dose of the comparator treatments was applied (IGlar 40 IU, IAsp 40 IU), with IDegLira dosing unchanged from the base case analysis (IDegLira 44.8 dose steps). In the second scenario, the observed trial doses were investigated during the analysis (i.e., doses were not adjusted using the statistical model in this sensitivity analysis). The doses were: IDegLira, 44.8 dose steps; IGlar, 67.6 IU; IAsp, 64.0 IU.
- Alternative Injection and SMBG Frequency in the Comparator Arm: A conservative analysis was conducted which assumed that patients in the IGlar + 3 × IAsp arm used only two needles (for subcutaneous injection) and two SMBG tests per day. No other parameters were changed in this analysis.
- Costs of Complications: The effect of over- or under-estimating the direct cost of treating diabetes-related complications was investigated in two scenarios. In the first, the cost of treating complications was increased by 10%, and in the second the cost was reduced by 10%.
- Hypoglycemia Disutilities: The impact of disutilities for severe and non-severe hypoglycemic events on outcomes was assessed by using alternative published values [37].
- Update to the CORE Diabetes Model: In February 2014, an update to the CORE Diabetes Model incorporating data from the UKPDS 82 study was released, and an analysis using this version of the model was run. While a validation study of the revised model has been published, the model proprietors suggest that the update is used in a sensitivity analysis, with the previous version being used in the base case.
- Probabilistic Sensitivity Analysis: Probabilistic sensitivity analysis (PSA) was performed using the predefined function in the CORE Diabetes Model. Cohort characteristics, treatment effects, and complication costs and utilities were sampled from distributions, and the simulation was run using a second order Monte Carlo approach. Cohorts of 1000 patients were run through the model 1000 times for the PSA, as results were not subject to random statistical variation with these settings.

Scenario Analysis

A scenario analysis was conducted to compare IDegLira with the combination of GLP-1 RA (liraglutide) added to basal insulin. As in the base case analysis, treatment effects applied in the first year of the analysis (Table 3) were based on data from the expanded pooled analysis [22]. In this scenario, patients receiving both IDegLira and liraglutide added to basal insulin were assumed to receive treatment for the first 5 years of the analysis and then intensify to basal–bolus therapy. On intensification to basal–bolus therapy the benefits in terms of HbA_{1c} and BMI were abolished, and hypoglycemia rates were based on the basal–bolus arm (as described above for the IDegLira treatment arm of the base case analysis).

Patients receiving both IDegLira and liraglutide added to basal insulin were assumed to use one SMBG test per day. The total annual per-patient cost (including drugs, needles, and SMBG testing) was CZK 66,006.10 for IDegLira versus CZK 58,993.81 for liraglutide added to basal insulin (based on current prices in May 2016 when the analysis was conducted). All other parameters in this analysis were unchanged.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

RESULTS

Base Case Analysis

Clinical benefits of treatment with IDegLira resulted from both a reduced incidence of diabetes-related complications over the 50-year time horizon of the model and a delayed mean time to onset of diabetes-related complications. Mean time to onset of any diabetes-related complication in the modeling analysis was approximately 0.4 years longer with IDegLira than with IGlar U100 + 3 × IAsp. Benefits were observed across all micro- and macrovascular complications included in the analysis.

IDegLira was associated with increased treatment costs (driven by the acquisition costs over the first 5 years of the analysis), but this was partially offset by cost savings as a result of avoided diabetes-related complications.

Table 3 Treatment effects applied in patients previously uncontrolled on basal insulin (IDegLira vs. liraglutide added to basal insulin)

Parameter	IDegLira	Liraglutide added to basal insulin
HbA_{1c} (%)	− 1.66 (0.96)	− 1.32* (0.96)
SBP (mmHg)	− 6.86 (13.20)	− 4.67* (13.20)
Total cholesterol (mg/dL)	− 10.13 (30.28)	− 12.66* (30.28)
HDL cholesterol (mg/dL)	+ 0.52 (6.79)	− 0.77 (6.79)
LDL cholesterol (mg/dL)	− 6.85 (23.83)	− 9.07 (23.83)
Triglycerides (mg/dL)	− 25.74 (103.71)	− 18.99 (103.71)
BMI (kg/m^2)	− 1.04 (1.34)	− 1.29* (1.34)
Severe hypoglycemia event rate (events/100 PYE)	0.84	0[a]
Non-severe hypoglycemia event rate (events/100 PYE)	125.05*	124.46

Values in table are presented as the mean with the SD in parenthesis
* statistically significantly different from IDegLira
[a] Significance could not be tested as there were zero events

Table 4 Base case analysis—IDegLira versus basal–bolus therapy

Parameters	IDegLira	Basal–bolus therapy	Difference
Discounted life expectancy (years)	13.57 (0.19)	13.46 (0.18)	+ 0.10
Discounted quality-adjusted life expectancy (QALYs)	8.69 (0.12)	8.38 (0.12)	+ 0.31
Discounted direct costs (CZK)	1,037,842 (25,466)	930,013 (25,147)	+ 107,829
ICER (life expectancy)	CZK 1,043,842 per life year gained		
ICER (quality-adjusted life expectancy)	CZK 345,052 per QALY gained		

Values in table are presented as the mean with the SD in parenthesis
CZK Czech Koruna, *ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life year

Treatment with IDegLira was associated with improvements in quality-adjusted life expectancy of 0.31 QALYs, at an additional cost of CZK 107,829 over a patient's lifetime, versus IGlar U100 + 3 × IAsp treatment (Table 4). IDegLira was associated with an ICER of CZK 345,052 per QALY gained versus IGlar U100 + 3 × IAsp, which falls below the commonly quoted WTP threshold of CZK 1,100,000 per QALY gained; therefore, IDegLira is likely to be considered cost-effective.

One-Way Sensitivity Analysis Results

Sensitivity analyses found that the outcomes projected in the present analysis were robust to changes in the input parameters and the assumptions used (Fig. 2 and ESM Appendix). IDegLira was likely to be cost-effective in all scenarios investigated, with all ICERs falling under the WTP threshold of CZK 1,100,000 per QALY gained.

Shortening the time horizon of the analysis had a notable impact on the calculated outcomes, with the clinical benefit reduced at 20 and 10 years, primarily due to the improvements in physiological parameters associated with IDegLira reducing the risk of long-term complications. Surprisingly, the increase in cost with IDegLira was smaller over reduced time horizons, likely due to the survival paradox, where greater survival in the IDegLira arm results in greater costs in later years. Shortening the time horizon to 10 years resulted in an ICER of CZK 413,391 per QALY gained.

Altering the discount rates used also reflected the long-term benefits with IDegLira. Reducing the discount rate led to a fall in the ICER to CZK 296,784 per QALY gained, while increasing the discount rate to 5% had the converse effect.

Abolishing each of the changes in physiological parameters associated with IDegLira revealed that the key drivers of improved clinical outcomes were reduced rates of minor hypoglycemia and improvements in BMI. Abolishing these differences between the treatment arms resulted in quality-adjusted life expectancy benefits of 0.20 and 0.22 QALYs, respectively. Applying only the statistically significant differences between the treatment arms resulted in an ICER of CZK 348,373 per QALY gained.

Applying an alternative HbA_{1c} progression with no increases applied at any stage of the analysis (attempting to replicate the legacy effect) resulted in improved incremental clinical outcomes and a smaller increase in costs, with the ICER falling to CZK 259,552 per QALY gained. Application of the UKPDS HbA_{1c} progression equation resulted in only small changes in the incremental differences between the treatment arms. These analyses show that the conclusions were robust to changes in assumptions around long-term changes in HbA_{1c}.

Using the upper 95% confidence interval of the HbA_{1c} change in the IDegLira arm resulted in an increased clinical benefit, with the ICER falling to CZK 328,310 per QALY gained. Applying the lower 95% confidence interval of the HbA_{1c} change in the IDegLira arm had the converse effect, with the ICER increasing to CZK 366,999 per QALY gained.

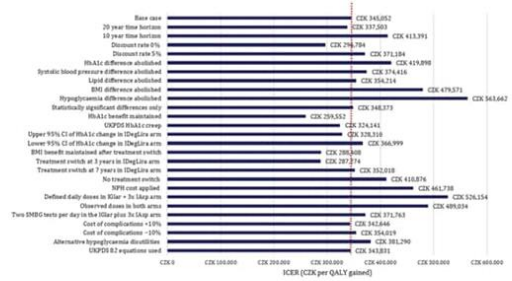

Fig. 2 IDegLira [fixed-ratio combination of the insulin analog degludec (IDeg) and the glucagon-like peptide-1 (GLP-1) receptor agonist (GLP-1 RA) liraglutide] versus basal–bolus therapy: sensitivity analysis results. Red dotted line shows the base case incremental cost-effectiveness ratio (ICER). The willingness-to-pay threshold in the Czech Republic at the time of analysis was CZK 1,100,000 per QALY gained. BMI Body mass index, CI confidence interval, CZK Czech Koruna, HbA_{1c} glycated haemoglobin, IGlar + 3 × IAsp, addition of insulin aspart to insulin glargine three times daily, NPH insulin intermediate-acting insulin, UKPDS 82 UK Prospective Diabetes Study

Maintaining the BMI benefit associated with IDegLira after treatment switching resulted in an increased clinical benefit, with only a small change in costs. An ICER of CZK 288,408 per QALY gained was calculated.

Changing the assumptions around treatment switching had a notable impact on both incremental clinical and cost outcomes, but variation in ICERs was relatively small. Maintaining patients on IDegLira for a longer period of time increased the incremental clinical benefit but increased the additional cost, while shortening the treatment duration had the converse effect. Assuming no treatment switching resulted in an ICER of CZK 410,876 per QALY gained.

Applying the cost of NPH insulin in the IGlar + 3 × IAsp arm lead to an increased ICER of CZK 461,738 per QALY gained. Applying defined daily doses or observed doses (i.e., not adjusted by the statistical model) resulted in an increased incremental cost difference, with increased ICERs. In the conservative analysis where patients receiving IGlar + 3 × IAsp used only two needles and two SMBG tests per day the ICER increased to CZK 371,763 per QALY gained.

Increasing the cost of treatment of diabetes-related complications resulted in a reduced increase in costs with IDegLira, while reducing the cost of treatment of diabetes complications had the converse effect. In these two analyses the ICERs varied from the base case by approximately CZK 4000 per QALY gained.

Use of alternative hypoglycemia disutilities resulted in only a small change in the quality-adjusted life expectancy benefit with IDegLira and only a small change in the ICER. Similarly, using the updated UKPDS risk equations resulted in only a small change in the calculated ICER.

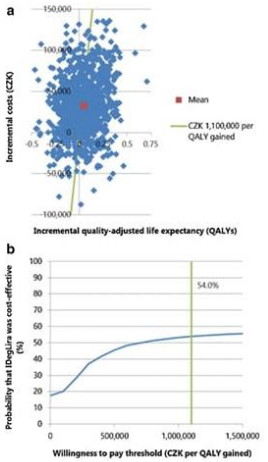

Fig. 3 Probabilistic sensitivity analysis for IDegLira versus basal–bolus therapy. **a** Cost-effectiveness scatterplot. **b** Cost-effectiveness acceptability curve

Probabilistic Sensitivity Analysis Results

The incremental cost-effectiveness scatterplot presents the incremental costs versus incremental effectiveness (QALYs gained) for IDegLira versus IGlar U100 + 3 × IAsp (Fig. 3a) and shows 1000 mean values, each from a cohort of 1000 patients run through the model with sampling from distributions around model input parameters. The majority (97.1%) of points fell in the upper right quadrant, revealing both increased effectiveness (i.e., incremental quality-adjusted life expectancy) and increased total costs for IDegLira compared with IGlar U100 + 3 × IAsp.

The data from the scatterplot were used to generate a cost-effectiveness acceptability curve (Fig. 3b). Based on this analysis, assuming a WTP threshold of CZK 1,100,000 per QALY gained, the modeling analysis indicated that there was a 54.0% probability that IDegLira was cost-effective versus IGlar U100 plus 3 × IAsp.

Scenario Analysis—IDegLira vs Liraglutide added to Basal Insulin

Treatment with IDegLira was associated with improvements in a quality-adjusted life expectancy of 0.05 QALYs, at an additional cost of CZK 33,231 over a patient's lifetime versus liraglutide added to basal insulin (Table 5). IDegLira was associated with an ICER of CZK 693,763 per QALY gained versus liraglutide added to basal insulin, which falls below the commonly quoted WTP threshold of CZK 1,100,000 per QALY gained; therefore, IDegLira is likely to be considered cost-effective.

Sensitivity analyses found that the outcomes projected in the present analysis were robust to changes in the majority of input parameters and the assumptions used (see ESM Appendix Table S4). IDegLira was likely to be cost-effective in most scenarios investigated, with ICERs falling under the WTP threshold of CZK 1,100,000 per QALY gained. The scenarios in which IDegLira was no longer cost-effective versus liraglutide added to basal insulin were when the time horizon was reduced to 10 years, the HbA_{1c} difference was abolished, defined daily doses were used for liraglutide added to basal insulin, and observed doses were used in both treatment arms. The parameter that had the largest impact on the ICER was abolishing the HbA_{1c} difference, identifying that the key driver of improved clinical outcomes with IDegLira versus liraglutide added to basal insulin was the greater reduction in HbA_{1c}.

DISCUSSION

Results from this long-term economic evaluation suggest that, from a public payer

Table 5 Base results for scenario analysis—IDegLira versus liraglutide added to basal insulin

Parameters	IDegLira	Liraglutide added to basal insulin	Difference
Discounted life expectancy (years)	13.56 (0.19)	13.51 (0.19)	+ 0.05
Discounted quality-adjusted life expectancy (QALYs)	8.77 (0.13)	8.72 (0.13)	+ 0.05
Discounted direct costs (CZK)	1,024,189 (26,092)	990,958 (25,453)	+ 33,231
ICER (life expectancy)	CZK 642,771 per life year gained		
ICER (quality-adjusted life expectancy)	CZK 693,763 per QALY gained		

Values in table are presented as the mean with the SD in parenthesis

perspective in the Czech Republic, for patients with T2DM uncontrolled on basal insulin, IDegLira is likely to be cost-effective versus IGlar U100 + 3 × IAsp (basal–bolus therapy), with an ICER of CZK 345,052 per QALY gained. This falls well below the commonly accepted WTP threshold in the Czech Republic of CZK 1,100,000 per QALY gained.

IDegLira was associated with improved clinical outcomes versus IGlar + 3 × IAsp. The key drivers of improved clinical outcomes in the IDegLira arm were reduced rates of hypoglycemia and reductions in BMI. Changes in these risk factors mainly affect the quality—rather than the duration—of life. However, reductions in HbA_{1c} and systolic blood pressure were also important in driving life expectancy benefits. These treatment differences resulted in a reduced incidence of diabetes-related complications and therefore impacted on the duration of life, quality of life, and direct costs. IDegLira was associated with increased mean direct costs compared with IGlar + 3 × IAsp, driven by the higher annual cost of IDegLira versus IGlar + 3 × IAsp over the first 5 years of the analysis. However, this increased direct cost was partially offset by cost savings through the lower need for treatment of diabetes-related complications as a result of improved treatment.

Sensitivity analyses found that the results were robust to changes in the input parameters and assumptions. All ICERs remained below the commonly quoted WTP threshold of CZK 1,100,000 per QALY gained. The highest ICER identified was CZK 563,662 per QALY gained, when the difference in hypoglycemia rate was abolished.

This study was designed to capture the most appropriate comparator for patients failing to achieve glycemic control on basal insulin therapy in the Czech Republic. The most common therapeutic adaptation for such patients in the Czech Republic is the addition of fast-acting prandial insulin and, therefore, we considered IGlar U100 + 3 × IAsp to be the most appropriate comparator in our analysis. However, the combination of GLP-1 RA and basal insulin is also included as an option in a recent guidance in the Czech Republic. Therefore, we also conducted a scenario analysis to evaluate the cost-effectiveness of IDegLira versus liraglutide added to basal insulin. In this latter scenario, IDegLira was associated with an ICER of CZK 693,763 per QALY gained, which also falls below the commonly quoted WTP threshold of CZK 1,100,000 per QALY gained, and thus likely to be considered cost-effective.

A potential limitation of the study was the reliance on relatively short-term clinical trial data to make long-term projections, a problem common to a number of health economic analyses. The uncertainty around making long-term projections from short-term data remains one of the essential principles of health economic modeling, and it remains arguably one of the best available options to inform decision-making in the absence of long-term clinical trial data. Every effort has been made in the present analysis to minimize any element of clinical doubt around the accuracy of such an approach, mainly by using an extensively published model of diabetes which has been validated against real-life data both on first publication and recently following a series of model updates [28, 38]. Despite certain limitations, projecting outcomes over patient lifetimes is recommended in guidelines for economic evaluation of interventions for patients with diabetes mellitus [39].

In the absence of head-to-head clinical trials, data to inform these analyses were derived from an indirect statistical pooled analysis. The use of evidence synthesis, such as the indirect comparison, using robust methodologies is becoming an increasingly important and accepted method for health technology assessment globally [40]. The methodology used in the pooled analysis is recognized by the European Network for Health Technology Assessment (EUNETHTA) guidelines on how to conduct indirect analyses [41] and has been used previously [42].

The fixed ratio combination of IDegLira utilizes the complimentary mechanisms of action of a basal insulin and a GLP-1 RA to achieve glycemic control while mitigating the risk of hypoglycemia and avoiding weight gain. IDegLira may also be advantageous with regard to treatment adherence as it is associated with a lower incidence of gastrointestinal side effects, such as nausea, than is typically observed with GLP-1 RAs, a likely result of the gradual increase in the dose of the liraglutide component of IDegLira during dose titration [43]. The use of GLP-1 RAs has been associated with a risk of developing acute pancreatitis; however, a meta-analysis investigating the use of GLP-1 RAs and pancreatitis found that neither liraglutide nor exenatide were associated with an increased risk of acute pancreatitis [44], and there have been few reported events of pancreatitis with IDegLira [19]. The once-daily IDegLira treatment regimen means that patients have a simple treatment option with reduced treatment complexity, with up to three fewer daily injections than basal–bolus regimens. The combination of IDeg and liraglutide in a single pen device means that patients will only need to perform a single dose adjustment, and resource use costs (e.g. needles and SMBG testing) will be lower than with basal–bolus therapy.

CONCLUSION

In the Czech Republic, IDegLira is an attractive alternative treatment option for patients with T2DM uncontrolled on basal insulin. In particular, IDegLira is associated with a reduced risk of hypoglycemia and weight gain versus basal–bolus therapy [21, 22], both of which are common obstacles to treatment intensification [21].

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All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

Data Availability. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Cost-Minimization Analysis of Metformin and Acarbose in Treatment of Type 2 Diabetes

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ABSTRACT

Background: Metformin is the first-line oral hypoglycemic agent for type 2 diabetes mellitus (T2DM) per international guidelines with proven efficacy, safety, and cost-effectiveness. However, little information comparing it with acarbose exists. **Objective:** To study the cost-effectiveness of metformin and acarbose—two extensively adopted agents—in treating T2DM. **Methods:** Cost-minimization analysis was conducted on the assumption that metformin and acarbose have equivalent clinical effectiveness. The cost of treatment was detected and evaluated from a payer's perspective. In sensitivity analyses, several clinical scenarios were developed according to clinical practices and physicians' prescribing behaviors in China. **Results:** Metformin can save annual treatment costs by 39.87% to 40.97% compared with acarbose. Under a wide range of assumptions on utilization profile and physician prescribing behavior, it saves costs by 19.83% to 40.97% in patients whose weight is 60 kg or less and by 39.87% to 70.49% in patients whose weight is more than 60 kg, which corroborates the results that metformin is more cost-effective than acarbose. **Conclusions:** Metformin appears to provide better value for money than does acarbose. Findings from this study are consistent with those from previous studies that metformin is undoubtedly the first choice in the management of T2DM, with significant glucose-lowering effects and low treatment costs.

Keywords: acarbose, cost-minimization, metformin, type 2 diabetes.

Introduction

Diabetes is one of the common chronic diseases worldwide [1]. China leads among the countries with the highest prevalence of diabetes. In 2010, the prevalence of diabetes in Chinese adults 18 years and older was 11.6% (113.9 million) [2]. Because of the long duration and expensive treatment, diabetes not only affects patients' quality of life but also brings a heavy economic burden to both the family and the society. A study on the epidemic and economic burden of diabetes in China [3] indicates that the average annual growth rate of direct medical cost of diabetes was 19.9% in recent years, which was higher than the gross domestic product and national health care expenditure growth over the same period, ranking the second in all surveyed chronic diseases.

Type 2 diabetes mellitus (T2DM) accounts for at least 90% of all cases of diabetes [4]. It has brought great burden in terms of health care cost and socioeconomic consequences, reaching $26.0 billion in 2007 in direct medical costs and predicted to be $47.2 billion by 2030 in China [5]. Glycemic control in patients with T2DM is directly related to the occurrence of diabetes-related complications and the extent of damage to target organs, and it is the key point in treating T2DM. When lifestyle interventions can no longer bring about glycemic control, oral hypoglycemic agents are the main methods used for the treatment of T2DM. Owing to the advances in T2DM treatment, there are many kinds of oral hypoglycemic agents available in the market. Each agent has its peculiarity in mechanism and site of action; thus, their glucose-lowering effects and treatment costs for patients vary significantly.

As a biguanide drug, metformin is the first-line oral hypoglycemic agent for T2DM in compliance with international guidelines with proven efficacy, safety, and cost-effectiveness [6–8], whereas acarbose, one of the α-glucosidase inhibitors, is recommended as one of the second-line drugs in the treatment of diabetes in China [7]. In use of oral antidiabetic drugs in China, metformin (53.7%) and α-glucosidase inhibitors (including acarbose, 35.9%), however, are both widely accepted and used either as monotherapy or in combination with other antidiabetic agents [9]. A possible reason for the popular use of acarbose may be its effect, which is superior in patients eating a relatively high carbohydrate diet, such as Chinese [10]. Little information exists, however, comparing metformin with acarbose in both clinical effectiveness and cost-effectiveness.

After a meta-analysis, it was found that glucose-lowering effects of metformin monotherapy and acarbose monotherapy are the same by direct comparison, while metformin monotherapy is a little better by indirect comparison [11]. This means that glucose-lowering effects of metformin monotherapy are at least as good as those of acarbose monotherapy. Thus, this study aimed to make an economic evaluation by using a cost-minimization analysis technique to see which drug is more cost-effective.

Methods

Estimation of the Cost

The perspective of the payer was used in this study because both drugs are covered by the payer. Cost was estimated on the basis of treatment schedules from the literature [12–19] and prices of both drugs in China; only direct medical costs were included. For metformin (brand name Glucophage, specification 500 mg × 20 tablets), the highest price set by the government is ¥29.2 and the lowest set by the market is ¥24.82; for acarbose (brand name Glucobay, specification 50 mg × 30 tablets), the highest and the lowest price is ¥74.2 and ¥61.92, respectively [20–23]. Both the lowest and highest prices were used to estimate the annual average treatment cost. Because both drugs are common oral hypoglycemic agents and tolerated well and have similar treatment efficacy and gastrointestinal adverse reactions, which can be alleviated by starting at a low dose and escalating the dose gradually [7,11,24–26], we, therefore, assume that patients taking both drugs have the similar frequency of doctor visits. Thus, we assume that the relevant costs in treating T2DM, such as doctor visit, diagnostic, inspection, and hospitalization cost, and so forth [27], can be set to be equivalent and not included in this study. All costs were based on 2014 prices and expressed in Renminbi (¥). No cost discounting was applied because all costs were measured by a period of 1 year.

Base-Case Identification

There is no fixed dosage regimen for the management of hyperglycemia in patients with T2DM with metformin or acarbose or any other pharmacologic agents [24,25]. Data on medication use and average dosage were derived from the direct comparison section of the meta-analysis [11–19], which directly compared the treatment effect of metformin and acarbose and showed their comparable efficacy in the Chinese population (1500 mg/d for metformin and 150 mg/d for acarbose).

Sensitivity Analysis

Because physicians' compliance with drug's instruction recommendations or national guidelines with regard to the initiation and monitoring of drug dosage in treating T2DM is unknown, in sensitivity analysis, several different clinical scenarios were developed after interviews with physicians treating diabetic patients, to illustrate potential clinical situations as well as to analyze the difference in annual average treatment costs with metformin and acarbose.

Based on physicians' prescribing behaviors in China and the potential increased risk for elevated serum transaminases in patients with low body weight [25], the usual maximum dose of acarbose is slightly different in different weight groups (150 mg/d for weight ≤ 60 kg and 300 mg/d for weight > 60 kg) [28–30]. Meanwhile, because of the difference in clinical prescribing habits and cognition of physicians in China, metformin also has two usual maximum doses (1500 and 2000 mg/d) in clinical practice, which is not strongly associated with patients' weight. Eight clinical scenarios, therefore, were developed according to different therapeutic regimens for patients with T2DM with different body weights to model different clinical conditions that may reflect real-world usage patterns of patients with T2DM. Scenario 1 considered all patients treated using only one oral drug (metformin or acarbose) at the initial dose. Scenarios 2, 5, and 6 involved patients who received only one oral drug (metformin or acarbose) at the usual maximum dose. Scenarios 3, 4, 7, and 8 simulated a situation that both drugs were titrated from the initial dose to the usual maximum dose gradually in patients with different body weights (Table 1). The common characteristics of scenarios 2 to 4 are that patients' weight is 60 kg or less and that of scenarios 5 to 8 is that patients' weight is more than 60 kg. Moreover, scenario 1 includes both weight groups (Table 1).

Results

Annual Average Treatment Cost of Metformin and Acarbose at Base Case

In base-case cost analysis, the annual treatment cost of metformin was ¥1358.90 while that of acarbose was ¥2260.08 when referring to the lowest price; the annual treatment cost of metformin and acarbose was ¥1598.70 and ¥2708.30 referring to the highest price, respectively. Under the same level of glycemic control, metformin could achieve annual cost savings by 39.87% (lowest price) or 40.97% (highest price) compared with acarbose (Table 2).

Annual Average Treatment Cost of Metformin and Acarbose at Different Scenarios

The annual treatment cost of metformin ranged from ¥452.97 to ¥2131.60 whereas that of acarbose ranged from ¥753.36 to ¥2708.30 at the four different scenarios (scenarios 1–4) in which patients' weight is 60 kg or less. Under these assumptions, metformin also minimizes the cost in all the four scenarios regardless of changes in daily dosage or medication cost, remaining a cost-saving strategy of 19.83% to 40.97% (Table 2).

The annual treatment cost of metformin ranged from ¥452.97 to ¥2131.60 whereas that of acarbose ranged from ¥753.36 to ¥5416.60 at the five different scenarios (scenario 1, and 5–8) in which patients' weight is more than 60 kg. For all the five scenarios, metformin administration was the lower cost strategy compared with acarbose, for which savings ranged from 39.87% to 70.49% (Table 2).

Discussion

Economic evaluation refers to the comparative analysis of alternative projects in terms of their costs and consequences by using principles and methods of economics. In the context of current health policy, with more and more governments trying to limit the escalation in health expenditure, there is an increasing need to find medical treatment strategies that are as effective but less costly. A pharmacoeconomic approach is commonly used to evaluate the health benefit of drug treatments to gain good value for money. Economic evaluation of medical products is particularly important in a country such as China, where for the inclusion of a drug in the national essential drugs list, the call in and out of a drug in the National Reimbursement Drug List, and the pricing of new drugs, patent medicines, and other drugs,

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Table 1 – Clinical scenarios for patients with T2DM with different body weight.

Scenario	Patient	Description
1	All weights	Metformin is maintained in initial dose (500 mg/d); acarbose is maintained in initial dose (50 mg/d).
2	Weight ≤ 60 kg	Metformin is maintained in usual maximum dose (2000 mg/d, given in divided doses); acarbose is maintained in usual maximum dose (150 mg/d, given in divided doses).
3	Weight ≤ 60 kg	Metformin is started at 500 mg/d for the first week and titrated up to 1000 mg/d given in divided doses in the second week and to 1500 mg/d given in divided doses from the third week onwards. Acarbose is started from 50 mg/d during the first week and titrated up to 100 mg/d given in divided doses in the second week and to 150 mg/d given in divided doses from the third week onwards.
4	Weight ≤ 60 kg	Metformin is started at 500 mg/d for the first week and titrated up to 1000 mg/d given in divided doses in the second week, to 1500 mg/d given in divided doses in the third week, and to 2000 mg/d given in divided doses from the fourth week onwards. Acarbose is started from 50 mg/d during the first week and titrated up to 100 mg/d given in divided doses in the second week and to 150 mg/d given in divided doses from the third week onwards.
5	Weight > 60 kg	Metformin is maintained in usual maximum dose (1500 mg/d, given in divided doses); acarbose is maintained in usual maximum dose (300 mg/d, given in divided doses).
6	Weight > 60kg	Metformin is maintained in usual maximum dose (2000 mg/d, given in divided doses); acarbose is maintained in usual maximum dose (300 mg/d, given in divided doses).
7	Weight > 60kg	Metformin is started at 500 mg/d for the first week and titrated up to 1000 mg/d given in divided doses in the second week and to 1500 mg/d given in divided doses from the third week onwards. Acarbose is started from 50 mg/d during the first week and titrated up to 100 mg/d given in divided doses in the second week, to 150 mg/d given in divided doses in the third week, and to 300 mg/d from the fourth week onwards.
8	Weight > 60 kg	Metformin is started at 500 mg/d for the first week and titrated up to 1000 mg/d given in divided doses in the second week, to 1500 mg/d given in divided doses in the third week, and to 2000 mg/d given in divided doses from the fourth week onwards. Acarbose is started from 50 mg/d during the first week and titrated up to 100 mg/d given in divided doses in the second week, to 150 mg/d given in divided doses in the third week, and to 300 mg/d from the fourth week onwards.

T2DM, type 2 diabetes mellitus.

Table 2 – The annual treatment cost of metformin and acarbose in patients with T2DM.

Scenario	Price*	Annual treatment cost (¥)		Cost difference (¥)†	Saving in annual cost (%)‡
		Acarbose	Metformin		
Base case	Lowest	2260.08	1358.90	901.18	39.87
	Highest	2708.30	1598.70	1109.6	40.97
Patients with T2DM with weight ≤ 60 kg					
Scenario 1	Lowest	753.36	452.97	300.39	39.87
	Highest	902.77	532.90	369.87	40.97
Scenario 2	Lowest	2260.08	1811.86	448.22	19.83
	Highest	2708.30	2131.60	576.7	21.29
Scenario 3	Lowest	2216.74	1332.83	883.91	39.87
	Highest	2656.36	1568.04	1088.32	40.97
Scenario 4	Lowest	2216.74	1759.74	457	20.62
	Highest	2656.36	2070.28	586.08	22.06
Patients with T2DM with weight > 60 kg					
Scenario 1	Lowest	753.36	452.97	300.39	39.87
	Highest	902.77	532.90	369.87	40.97
Scenario 5	Lowest	4520.16	1358.90	3161.26	69.94
	Highest	5416.60	1598.70	3817.9	70.49
Scenario 6	Lowest	4520.16	1811.86	2708.3	59.92
	Highest	5416.60	2131.60	3285	60.65
Scenario 7	Lowest	4346.78	1332.83	3013.95	69.34
	Highest	5208.84	1568.04	3640.8	69.90
Scenario 8	Lowest	4346.78	1759.74	2587.04	59.52
	Highest	5208.84	2070.28	3138.56	60.25

T2DM, type 2 diabetes mellitus.

* Lowest, the lowest set by market; highest, the highest price set by government.

† Cost difference = annual cost of acarbose − annual cost of metformin.

‡ Saving in annual cost = (annual cost of acarbose − annual cost of metformin) × 100/annual cost of acarbose.

it is now, by law, recommended that technical evaluation for the drugs be conducted by using evidence-based medicine and pharmacoeconomics approaches [31–34].

This study examined the costs of metformin and acarbose in the treatment of patients with T2DM. We used the cost-minimization analysis technique under the hypotheses that key clinical outcomes and adverse effects of both drugs are effectively equivalent based on results from a previous meta-analysis study [11]. Our results show that metformin seems to be more cost-effective than acarbose.

In economic evaluation, it is difficult to accurately measure the study variables, and each medication therapy may bring different treatment costs when applied among different population or medical institutions; therefore, it is important to verify the effect of basic assumptions on study results. Thus, we developed eight scenarios, in sensitivity analyses, to mirror the real-life cost profile. The results are consistent with the base-case analysis, corroborating that metformin is more cost-effective than acarbose. Our results, however, may represent a cost-effective advantage for metformin only if differences in dosage adjustment and monitoring were observed in a real clinical practice and underlying hypotheses mentioned above are true.

Results from this study confirm findings from several economic evaluation studies conducted in China, comparing metformin monotherapy with acarbose monotherapy in the treatment of T2DM. The studies reported that metformin was cost-effective than acarbose for treating T2DM [35–41], and particularly, it was superior to acarbose in controlling fasting blood glucose [42–46]. As the course of T2DM prolongs, any single therapy may find it difficult to effectively control the blood glucose level of patients with T2DM, and then there is a need to use combination therapies to strengthen glycemic control in clinical practice. In this context, several studies assessing the comparative efficacy and cost of metformin and acarbose from the perspective of drug combination also indicate that metformin combination therapy is still a preferable therapeutic regimen compared with acarbose combination therapy [47–50]. Nevertheless, the reliability of these evaluation results might be constrained attributable to small sample sizes (range 87–705) in their basal clinical trials; thus, these findings should be considered with caution. Furthermore, a review of the economic evaluation of metformin hydrochloride and acarbose suggests that they have a similar role in prolonging the life of patients, improving the cardiovascular disease, and preventing or delaying the onset of T2DM [51]. Metformin hydrochloride is a preferred treatment for patients with T2DM, with a higher efficiency in reducing fasting blood glucose and minimum cost compared with other hypoglycemic drugs. Although acarbose is good at reducing postprandial blood glucose, it has a higher cost [51]. Moreover, in patients with impaired glucose tolerance, metformin demonstrates a better value for money [51]. Metformin is more cost-effective not only in treating T2DM but also in preventing the onset of diabetes compared with acarbose [52,53].

This study was conducted from a payer's perspective, and the indirect cost related to the T2DM treatment was not taken into account. Direct medical costs theoretically consist of fees for doctor visit, medication cost, diagnostic cost, inspection cost, hospitalization cost, transport cost, and so forth [27]. However, in this study, we estimated only the drug cost, not other costs because we assumed that other costs are the same in the two treatment groups. This study, furthermore, considers only a single monotherapy for 1 year; however, in clinical practice, because of the complexity of diabetes, drug combination therapy is common and patients may switch drug, which can have an impact on the cost; over a longer period, more complications related to diabetes, including microvascular and macrovascular disease, may occur [6], which can also add treatment costs. Thus, more studies are needed to understand the comprehensive annual costs to provide disease burden information for guiding decision making of resource allocation.

Regardless of these limitations, our study has a noteworthy strength that it is the first economic evaluation focusing on the comparison of metformin with acarbose in T2DM treatment, which is conducted on the basis of results from a meta-analysis study with large sample sizes and adequate clinical data.

Conclusions

Metformin appears to provide better value for money than does acarbose. Findings from this study are consistent with previous studies that metformin is undoubtedly the first choice in the management of T2DM, with significantly glucose-lowering effects and low treatment costs.

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Cost-effectiveness analysis of metformin +dipeptidyl peptidase-4 inhibitors compared to metformin+sulfonylureas for treatment of type 2 diabetes

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Abstract

Background: Patients with type 2 diabetes (T2D) typically use several drug treatments during their lifetime. There is a debate about the best second-line therapy after metformin monotherapy failure due to the increasing number of available antidiabetic drugs and the lack of comparative clinical trials of secondary treatment regimens. While prior research compared the cost-effectiveness of two alternative drugs, the literature assessing T2D treatment pathways is scarce. The purpose of this study was to evaluate the long-term cost-effectiveness of dipeptidyl peptidase-4 inhibitors (DPP-4i) compared to sulfonylureas (SU) as second-line therapy in combination with metformin in patients with T2D.

Methods: A Markov model was developed with four health states, 1 year cycle, and a 25-year time horizon. Clinical and cost data were collected from previous studies and other readily available secondary data sources. The incremental cost-effectiveness ratio (ICER) was estimated from the US third party payer perspective. Both, costs and outcomes, were discounted at a 3% annual discount rate. One way and probabilistic sensitivity analyses were performed to evaluate the impact of uncertainty on the base-case results.

Results: The discounted incremental cost of metformin+DPP-4i compared to metformin+SU was $11,849 and the incremental life-years gained were 0.61, resulting in an ICER of $19,420 per life-year gained for patients in the metformin+DPP-4i treatment pathway. The ICER estimated in the probabilistic sensitivity analysis was $19,980 per life-year gained. Sensitivity analyses showed that the results of the study were not sensitive to changes in the parameters used in base-case.

Conclusions: The metformin+DPP-4i treatment pathway was cost-effective compared to metformin+SU as a long-term second-line therapy in the treatment of T2D from the US health care payer perspective. Study findings have the potential to provide clinicians and third party payers valuable evidence for the prescription and utilization of cost-effective second-line therapy after metformin monotherapy failure in the treatment of T2D.

Keywords: Cost-effectiveness analysis, Type 2 diabetes, Costs, Outcomes, Life years gained, Metformin, Sulfonylureas, Dipeptidyl peptidase-4 inhibitors

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Background

Diabetes mellitus is one of the most prevalent and costly chronic diseases in the United States (US). In 2012, 9.3% of the US population had diabetes mellitus [1]. In that year 2012, the health care cost of diagnosed diabetes in the US totaled $245 billion [2]. The US market of antidiabetic products reached $43.9 billion in 2015 (a 109.0% increase from $21.0 billion in 2011) [3]. The number of prescriptions for antidiabetic drugs totaled 211 million in 2015 (compared to 174 million in 2011) [3]. In 2015, insulin glargine recombinant was the top fifth drug by sales in the US totaling $5.8 billion (241.2% increase compared to 2011) [3]. Sitagliptin was the top tenth prescription drug by sales reaching $4.2 billion in 2015 (a 90.9% increase compared to 2011) [3]. As of December 31, 2015, there were 27 unique non-insulin antidiabetic drugs, belonging to 12 therapeutic classes, including 5 modified formulations and 18 fixed-dose combinations of active ingredients, available in the US market [4].

Metformin has a well-established long-term post-marketing evidence of effectiveness and safety [5–7]. While there is a general consensus about the use of metformin as first-line therapy for type 2 diabetes (T2D) [5–7]; there is a vigorous debate about best second-line treatment regimen [8]. Sulfonylureas (SU) are a common second-line therapy due to their fast onset on blood glucose lowering [9, 10]. However, safety related concerns, including risk of hypoglycemia and weight gain, have been raised [9, 10]. Dipeptidyl peptidase-4 inhibitors (DPP-4i) are newer drugs with lower risk of hypoglycemia and weight gain but lower glycemic lowering effect than SU [10, 11]. In addition, DPP-4i are costlier than SU.

Two previous studies explored the cost-effectiveness of SU compared to DPP-4i as second-line therapy after metformin failure in the US. Study findings were inconclusive. Bergenheim et al. (2012) [12] assessed the lifetime cost-effectiveness of metformin+SU and metformin +DPP-4i in T2D using data from 52-week randomized controlled trial [9]. The authors concluded that DPP-4i was a cost-effective second-line therapy after metformin failure in the US. Zhang et al. (2014) [8] compared the medication cost and effectiveness of metformin+SU, DPP-4i, and glucagon-like peptide-1(GLP-1) receptor agonists as the second-line therapy until first diabetes-related complication or death. The authors found that metformin+SU resulted in similar outcomes but lower drug costs compared to other two comparators.

Bergenheim et al., (2012) did not consider insulin treatment after second-line failure; whereas, Zhang et al., (2014) included insulin treatment as third-line in their analyses. Furthermore, Bergenheim et al., (2012) included drug cost and diabetes related health care costs in their economic evaluation; whereas, Zhang et al., (2014) did not assess health care costs associated with diabetic complications, which often pose a significant economic burden on patients with T2D [1].

Additionally, a study conducted by Langer et al., (2013) [13] assessed the short-term cost-effectiveness of metformin+sitagliptin (i.e., DPP-4i inhibitor class) compared to metformin+liraglutide (i.e., GLP-1 receptor agonists) based on data derived from a 26-week randomized, controlled trial conducted by Pratley et al., (2010) [14]. The study time horizon was only 1 year. Authors found that mean cost per patient reaching target glycated hemoglobin (A1c) was lower for liraglutide than sitagliptin. Langer et al., (2013) included only drug costs in their analyses.

Prior research compared short-term cost-effectiveness of two alternative drugs for treatment of T2D. To the best of authors' knowledge, no previous US studies assessed the cost-effectiveness of alternative T2D treatment pathways over a patient's lifetime. Thus, this study assessed the long-term cost-effectiveness of dipeptidyl peptidase-4 inhibitors compared to sulfonylureas as second-line therapy for the treatment of T2D. This study has the potential to provide clinicians and third party payers with new perspectives on the cost-effectiveness of long-term treatment pathways for T2D.

Methods

Therapeutic alternatives

Most patients with T2D take one or more drugs in addition to metformin monotherapy to control their blood glucose levels and eventually, will initiate insulin therapy alone or in combination with other non-insulin antidiabetic drugs when previous alternatives fail. In the scenario analysis, there were two different treatments pathways. Both pathways started with metformin monotherapy, the most common treatment. Patient used metformin+DPP-4i or metformin+SU as second-line therapy when metformin monotherapy failed. In addition, both treatment pathways added basal insulin therapy in patients with T2D when combination therapy failed.

Markov model

A Markov model constructed in Microsoft Excel 2013 software was based on current T2D treatment guidelines [5, 6]. The Markov model had four states (Fig. 1). In the first state, patients used metformin monotherapy. Patients could remain in the first state or transition to the second state. In the second state, either DPP-4i or SU was added to metformin as second-line therapy. Likewise, patients could remain in the second state or transition to the third state where basal insulin was added to their current therapy as third-line therapy. Patients in those three states could transition anytime to death (i.e., absorbing state). We assumed that patients initiated metformin monotherapy at age

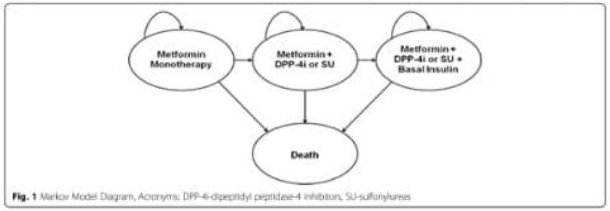

Fig. 1 Markov Model Diagram, Acronyms: DPP-4i-dipeptidyl peptidase-4 inhibitors, SU-sulfonylureas

60 years with a time horizon of 25 years (i.e., 60–85 years old). The cycle duration was 1 year [15].

Health outcomes and cost

Health outcomes data were collected from the literature (Table 1). Treatment failure rates obtained from previous studies were used to determine the annual probability of transitioning from metformin monotherapy to oral antidiabetic drug (OAD) dual therapy and from OAD dual therapy to OAD dual therapy+basal insulin states. Kahn et al., (2006) found that 21% of patients failed to achieve their therapeutic goals after 5 years in metformin monotherapy [16]. In addition, Rascati et al., (2013) estimated that 23.6% of patients using metformin+SU dual therapy progressed to OAD dual therapy+basal insulin after 59 months in treatment [17].

Parchman and Wang, (2012) found that the rate of insulin initiation had a statistically significant and positive association with the A1c increasing rate [18]. More specifically, Bergenheim et al., (2012) [12] found that patients using metformin+DPP-4i had four times lower A1c increasing rates than those using metformin+SU. Thus, we assumed that the annual treatment failure rate of metformin+DPP-4i was four times lower than metformin+SU.

Death rates for 60 to 70 years old, 71 to 80 years, and 81 to 85 years old groups were derived from the literature [19]. The hazard ratios of death in patients using metformin+SU and metformin+DPP-4i were also drawn from the literature [20]. Hypoglycemia probabilities in patients using metformin+SU and metformin+DPP-4i were extracted from the results of a 52-week randomized clinical trial [9]. We considered only severe hypoglycemia and hypoglycemia events requiring medical assistance to estimate direct health care costs. The probability of severe hypoglycemia for a patient using OAD + basal insulin was collected from the ORIGIN trial [21]. Weight gain data in patients using SU were derived from a previous study [12]. We assumed that use of metformin, DPP-4i and basal insulin were not associated with a significant weight gain [10].

Likewise, annual cardiovascular complication rates (i.e., myocardial infarction, heart failure and stroke) in patients using metformin monotherapy, OAD dual therapy, and OAD-basal insulin therapy for each health state described in the Markov model were derived from previous published clinical trial studies [11, 16, 21]. We assumed that the probability of treatment failure, hypoglycemia and cardiovascular complications remained constant through the study period with the exception of death rates which gradually increase with age. The proportion of patients in each state and cycle was calculated using the transition matrix (Tables 2 and 3).

The main study outcome was the number of life-years gained over the study time horizon. In order to estimate life-years gained, all life-years for patients in every state, with the exception of death, were aggregated by year and discounted. The incremental life-years gained were estimated as the difference in life-years gained between the two interest therapeutic alternatives metformin+DPP-4i and metformin+SU.

Direct health-care costs related to T2D, which included drug costs and treatment costs for diabetes related medical events such as hypoglycemia, weight gain and cardiovascular events were obtained from the US health care payer perspective. Direct health care cost input data were derived from the literature (Table 4). Indirect and intangible costs related to the disease were not included in the study model.

Antidiabetic drug costs data were collected from the National Average Drug Acquisition Cost (NADAC) dataset [22]. We used generic NADAC for metformin and SU (glipizide). The cost of DPP-4i was estimated as the average NADAC of sitagliptin, saxagliptin, linagliptin, and alogliptin. We also used the NADAC for basal insulin glargine pen type. Needle cost for insulin glargine pen was estimated at 80% of the average wholesale price (AWP). AWP data were derived from the online version

Table 1 Health outcomes used in study model

Variables (Annual Rate)	Value[a]	References
Treatment failure		
Metformin monotherapy	0.046	Kahn et al., 2006 [16]
Metformin+dipeptidyl peptidase-4 inhibitor	0.013	Rascati et al., 2013 [17] and Bergenheim et al., 2012 [12]
Metformin+sulfonylurea	0.053	Rascati et al., 2013 [17]
Death rate		
60–70 years	0.021	Zhuo et al., 2014 [19]
71–80 years	0.051	Zhuo et al., 2014 [19]
Over 81 years	0.107	Zhuo et al., 2014 [19]
Death hazard ratio of Metformin +SU to Metformin+DPP-4i	1.850	Morgan et al., 2014 [20]
Hypoglycemia		
Severe hypoglycemia among patients with Metformin+SU	0.016	Goke et al., 2010 [9]
Hypoglycemia with medical assistance among patients with Metformin+SU	0.009	Goke et al., 2010 [9]
Severe hypoglycemia among patients with insulin glargine	0.010	The Origin Trial Investigators, 2012 [21]
Weight gain in the first year after starting SU	0.510	Bergenheim et al., 2012 [12]
Myocardial infarction		
Metformin monotherapy	0.004	Kahn et al., 2006 [16]
Metformin+dipeptidyl peptidase-4 inhibitor	0.004	Gitt et al., 2013 [11]
Metformin+sulfonylurea	0.008	Gitt et al., 2013 [11]
Insulin glargine	0.009	The Origin Trial Investigators, 2012 [21]
Heart failure		
Metformin monotherapy	0.003	Kahn et al., 2006 [16]
Metformin+dipeptidyl peptidase-4 inhibitor	0.017	Gitt et al., 2013 [11]
Metformin+sulfonylurea	0.020	Gitt et al., 2013 [11]
Insulin glargine	0.009	The Origin Trial Investigators, 2012 [21]
Stroke		
Metformin monotherapy	0.003	Kahn et al., 2006 [16]
Metformin+dipeptidyl peptidase-4 inhibitor	0.002	Gitt et al., 2013 [11]
Metformin+sulfonylurea	0.020	Gitt et al., 2013 [11]
Insulin glargine	0.009	The Origin Trial Investigators, 2012 [21]

[a] Probability during certain period was converted to the rate per 1 year using following equation. (The rate was assumed to be constant over that period) $Rate = 1-(\frac{\text{1-year probability - probability change rate}}{\text{initial probability}})$

of the RedBook [23]. Annual prescription drug cost was calculated based on the defined daily dose (DDD) from WHO Collaborating Centre for Drug Statistics Methodology [24]. The direct health care cost in each state, with the exception of death, was estimated for each year through the study time horizon. Base-case health care costs in each state was calculated multiplying the probability of each episode and unit cost (Table 5). All costs were adjusted to 2015 US dollars using the all urban consumers, not seasonally adjusted, US city average, all items, consumer price index (CPI) [25]. Both costs and outcomes were discounted at a 3% annual discount rate.

Cost-effectiveness analysis

The cost-effectiveness analysis (CEA) of metformin +DPP-4i vs. metformin+SU in patients with T2D was conducted from the US health care payer perspective. The cost and life-years gained over the 25-year time horizon were estimated for each treatment pathway. A cost-effectiveness ratio (CER) was employed to calculate the cost per life-year gained for each treatment strategy. The lowest cost per life-year treatment was considered as the reference therapy. When a treatment had a greater cost and effectiveness in relation to the reference an incremental cost-effectiveness ratio was performed to determine the additional cost to obtain one life-year. Incremental cost-effectiveness ratio (ICER) was estimated for metformin+DPP-4i compared to metformin+SU.

One-way and probabilistic sensitivity analyses

The impact of parameter uncertainty was explored by one-way sensitivity analysis on each model parameter. Results of the one-way sensitivity analysis were expressed as tornado charts. Values for treatment failure rates, hypoglycemia events probabilities, weight gain rates, cardiovascular events rates, and costs were changed by ±25% from the base-case. The cost of insulin glargine was changed by ±20%. Death rates and the death hazard ratios were changed by ±10%. The one-way sensitivity analysis was also conducted to compare differences in study results using 20 and 30 year time horizons. The sensitivity analyses also included a scenario in which there was no difference in cardiovascular event rates after 2 years from initiation of metformin+DPP-4i and metformin+SU [26, 27].

Inzucchi et al., (2015) found that the mean (standard deviation) age at the start of the antidiabetic treatment was 57.4 (11.7) years [28]. The average time to insulin initiation was 1.94–20.7 years depending on basal treatment. Machado-Alba et al., (2015) found that mean age at the start of oral antidiabetic therapy in patients with type 2 diabetes mellitus was 63.4 years [29]. After 5 years, 26.1% initiated insulin therapy. Roussel et al., (2016) found that the average age (standard deviation) of insulin therapy initiation in patients with type 2 diabetes mellitus (T2DM) was 67.5 (14.2) years [30]. In one-way sensitivity analyses, we changed the patient age at start of the antidiabetic treatment metformin monotherapy from 60 years in the base case to 55 and 65 years.

Table 2 Transition matrix for the treatment pathway metformin+dipeptidyl peptidase-4 inhibitor

		To t + 1			
		Metformin monotherapy	Metformin +DPP-4i	Metformin +DPP-4i + Basal insulin	Death
From t	Metformin monotherapy	#	0.046	0	60–70 years; 0.021 71–80 years; 0.051 81–85 years; 0.107
	Metformin +DPP-4i	0	#	0.013	60–70 years; 0.021 71–80 years; 0.051 81–85 years; 0.107
	Metformin +DPP-4i + Basal insulin	0	0	#	60–70 years; 0.021 71–80 years; 0.051 81–85 years; 0.107
	Death	0	0	0	1

Acronyms: DPP-4i dipeptidyl peptidase-4 inhibitors

A probabilistic sensitivity analysis was conducted to investigate the combined impact of uncertainty of the variables included in the analysis. Random values were drawn from the chosen distributions as a second-order Monte-Carlo simulation of 1000 patients to estimate the mean and 95% confidential intervals (CI) of costs and life-years gained. All parameters in the model had correspondingly appropriate distributions. Costs were randomly drawn from a gamma distribution; hazard ratio were randomly sampled from a lognormal distribution. Likewise, binominal data, such as hypoglycemia probabilities and cardiovascular event rates were randomly drawn from a beta distribution. Multinomial data, such as transition probabilities in the metformin monotherapy and the OAD dual therapy states, were randomly sampled from a Dirichlet distribution [31].

The ICER was recalculated based on the patient age at start of the antidiabetic treatment, the average incremental costs and life-years gained derived from the probabilistic sensitivity analysis. The simulation output was presented using a cost-effectiveness plane. A cost-effectiveness acceptability curve (CEAC) was also plotted to summarize the uncertainty in the cost-effectiveness estimates.

Results

Base-case analysis

Diabetic-related annual average costs and life-years gained after discounting were $18,853 and 12.42 years, respectively for patients in the metformin+DPP-4i treatment pathway. Patients in the metformin+SU treatment pathway incurred in a lower annual average costs per patient ($7004) and gained on average a lower number of life-years (11.81 years) (Table 6). The incremental costs and life-years gained for metformin+DPP-4i compared to metformin+SU treatment pathways were $11,849 and 0.61 years, respectively. Thus, the ICER was $19,420 per life-year gained for patients in the metformin+DPP-4i treatment pathway.

One-way and probabilistic sensitivity analyses

One-way sensitivity analysis was conducted by varying the range of values in the base-case to determine potential impacts on the results. The percentage changes in ICER from base-case are presented in the tornado graph (Fig. 2). Time horizon, death hazard ratio and age at start of metformin monotherapy, and death rate parameters in the model had largest impact on the model results. The results of the analysis did not change significantly when varying estimates used in the base-case scenario (Table 7). Results for the base-case scenario were not sensitive to changes in the costs of insulin glargine, treatment failure rates, costs and rates of cardiovascular events, or the costs and probabilities of severe hypoglycemia, and weight gain. Results for the base-case scenario were not sensitive either to changes in the cardiovascular event rates of metformin+DPP-4i and metformin+SU.

Table 3 Transition matrix for the treatment pathway metformin+sulfonylureas

		To t+1			
		Metformin monotherapy	Metformin +SU	Metformin +SU + Basal insulin	Death
From t	Metformin monotherapy	#	0.046	0	60–70 years; 0.021 71–80 years; 0.051 81–85 years; 0.107
	Metformin +SU	0	#	0.053	60–70 years; 0.021 × 1.85 (HR) 71–80 years; 0.051 × 1.85 (HR) 81–85 years; 0.107 × 1.85 (HR)
	Metformin +SU + Basal insulin	0	0	#	60–70 years; 0.021 71–80 years; 0.051 81–85 years; 0.107
	Death	0	0	0	1

Acronyms: SU-sulfonylureas, HR-hazard ratio

Table 4 Direct health care annual costs (2015 USD)

	Average annual costs	References
Health care costs (per episode/year)		
Myocardial infarction	$18627	Bergenheim et al., 2012 [12]
Heart failure	$14118	Bergenheim et al., 2012 [12]
Stroke	$7939	Bergenheim et al., 2012 [12]
Hypoglycemia events requiring medical assistance	$199	Bergenheim et al., 2012 [12]
Severe hypoglycemia event	$146	Bergenheim et al., 2012 [12]
Weight gain	$289	Bergenheim et al., 2012 [12]
Drug cost (per patient/year)		
Metformin, generic drug	$24	NADAC (January 2015) [22]
Dipeptidyl peptidase-4 inhibitor, brand	$3500 ($3401; $3599)	NADAC (January 2015) [22]
Sulfonylurea (glipizide), generic	$16	NADAC (January 2015) [22]
Insulin glargine, brand	$3646	NADAC (January 2015) [22]

All drug costs and direct health-state costs were expressed in 2015 US dollars ($) per patient/year

The ICER increased to $24,250 per life-year gained (+ 24.3%) when the time horizon decreased to 20 years. Conversely, the ICER decreased to $17,580 per life-year gained (− 9.8%) when the time horizon increased to 30 years. In addition, a 10% decrease in the death hazard ratio resulted in a 21.9% increase in the ICER ($23,760). A 10% increase in the death hazard ratio resulted in a 14.0% decrease in the ICER ($16,760). Assuming that patients start metformin monotherapy at age of 55 increased ICER to $21,360 (9.6%); whereas, starting antidiabetic treatment at age of 65 decreased ICER to $18,120 (− 7.1%).

The average results of the probabilistic sensitivity analysis yielded $11,786 incremental costs and 0.59 incremental life-year gained for patients using metformin +DPP-4i compared to alternative metformin+SU treatment pathway (Table 8). The ICER in the probabilistic sensitivity analysis was $19,980 per life-year gained. The difference between the probabilistic sensitivity analysis and the base-case strategy was $63 in incremental costs and 0.02 additional life-years gained.

The uncertainty surrounding the expected costs and outcomes associated with metformin+DPP-4i compared with metformin+SU is illustrated in Fig. 3. The incremental cost-effectiveness plane shows the trade-offs in the northeast (i.e., positive costs and positive effects) and southeast quadrants (i.e., negative costs and positive effects).

The CEAC indicates that metformin+DPP-4i and metformin+SU would have the same probability of being the most cost-effective treatment for a WTP threshold of $12,500 per life-year gained; after exceeding this threshold the probability of metformin+DPP-4i being the most cost-effective treatment pathway approaches to 1 (Fig. 4).

Discussion

This study assessed the long-term cost-effectiveness of metformin+DPP-4i compared with metformin+ SU treatment pathways as second-line therapy from the US health care payer perspective. In the base-case results, the total costs and life-years gained were higher for metformin+DPP-4i than for the metformin+SU treatment pathway.

The results from the probabilistic sensitivity analyses were similar to those of the base-case results. The results of the one-way sensitivity analysis showed that the main factors impacting on the ICER were time horizon

Table 5 Base-case direct health care cost results of five treatment strategies

	Medical Costs	Costs per Hypoglycemia Event	Costs per Cardiovascular Events	Weight Gain Costs (transition costs[a])	Total Costs (without transition costs[a])
Metformin monotherapy	$24	$0	$141	$0	$165
Metformin+DPP-4i	$3524	$0	$330	$0	$3854
Metformin+DPP-4i + Basal insulin	$7170	$1	$366	$0	$7537
Metformin+SU	$40	$4	$441	$148	$486
Metformin+SU + Basal insulin	$3686	$1	$366	$0	$4054

Acronyms: DPP-4i dipeptidyl peptidase-4 inhibitors, SU-sulfonylureas
[a] Transition cost was added only one time when patients transitioned from the metformin monotherapy state to the metformin+SU state

Table 6 Base-case cost and effectiveness results of treatment strategies (per patient)

Discounted (3% annual discount rate)					
Second-line agent add-on to Metformin	Total		Incremental		
	Costs	LYs gained	Costs	LYs gained	ICER
Sulfonylurea	$7004	11.81			
Dipeptidyl peptidase-4 inhibitor	$18853	12.42	$11849	0.61	$19420
Undiscounted					
Sulfonylurea	$10501	15.68			
Dipeptidyl peptidase-4 inhibitor	$28013	16.70	$17512	1.02	$17170

All costs were expressed in 2015 US dollars ($)
Acronyms: LY-Life-year, CER-cost-effectiveness ratio (equal to cost/LY), ICER-incremental cost-effectiveness ratio (equal to incremental cost/incremental LYs)

and death hazard ratio from metformin+SU to metformin+DPP-4i. The probability that the DPP-4i treatment pathway would become the cost-effective alternative compared to metformin+SU increases as the WTP per life-year threshold increases. When the WTP per life-year equals $12,500 per life-year, the probability of the DPP-4i treatment pathway to be the most cost-effective alternative become 0.5.

The results of this study differ from two previous cost-effectiveness studies conducted in the US that compared metformin+DPP-4i and metformin+SU as a second line therapy. Bergenheim et al., (2012) compared metformin +saxagliptin with metformin+glipizide for the treatment of T2D [12]. The authors concluded that metformin +DPP-4i was a cost-effective second-line therapy in the US. Some methodological differences between Bergenheim et al., (2012) and this study are worth mentioning. Unlike this study, Bergenheim et al., (2012) did not include metformin monotherapy as the base-case therapy in T2D treatment. They did not consider either the treatment alternative OAD + insulin after metformin+SU and metformin+DPP-4i treatment failure. Bergenheim et al., (2012) considered the use of insulin as the rescue therapy when the A1c level was higher than 7.5%. They set up the patient lifetime as the study time horizon and used a Cardiff Long-term Cost Utility Model for the cost-effectiveness estimation. Bergenheim et al., (2012) estimated metformin+saxagliptin treatment pathway had a $2772 higher costs (2009 USD) and 2.65 greater QALYs (ICER was $1047 per QALY) compared to metformin+glipizide alternative. A life-time horizon allows to better understand the burden of the disease on patients with T2D inclusive of all treatment alternatives and related costs.

In addition, the difference in costs between Bergenheim et al., (2012) and this study is driven by the difference in the generic DPP-4i prices estimation. In this study we used NADAC prices of branded DPP-4i. Conversely, Bergenheim et al., (2012) assumed that generic DPP-4i

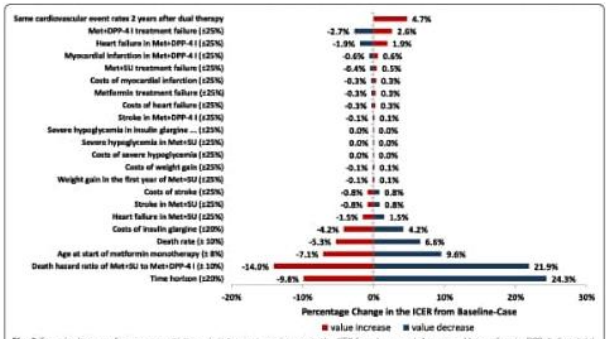

Fig. 2 Tornado diagram of one-way sensitivity analysis (percentage changes in the ICER from base-case). Acronyms: Met-metformin, DPP-4i-dipeptidyl peptidase-4 inhibitor, SU-sulfonylurea

Table 7 Results of one-way sensitivity analyses for base-case scenario

	Values	Estimated ICER
Base Case		$19420
Death hazard ratio of Met+SU to Met+DPP-4i	1.67 (−10%)	$23760
Death hazard ratio of Met+SU to Met+DPP-4i	2.04 (+ 10%)	$16760
Metformin treatment failure	0.035 (−25%)	$19440
Metformin treatment failure	0.058 (+ 25%)	$19560
Met+DPP-4i treatment failure	0.010 (−25%)	$18970
Met+DPP-4i treatment failure	0.017 (+ 25%)	$20010
Met+SU treatment failure	0.040 (−25%)	$19410
Met+SU treatment failure	0.067 (+ 25%)	$19590
Severe hypoglycemia in Met+SU	0.012 (−25%)	$19500
Severe hypoglycemia in Met+SU	0.020 (+ 25%)	$19500
Severe hypoglycemia in insulin glargine triple therapy	0.008 (−25%)	$19500
Severe hypoglycemia in insulin glargine triple therapy	0.013 (+ 25%)	$19500
Weight gain in the first year of Met+SU	0.383 (−25%)	$19520
Weight gain in the first year of Met+SU	0.638(+ 25%)	$19470
Myocardial infarction in Met+DPP-4i	0.003(−25%)	$19380
Myocardial infarction in Met+DPP-4i	0.005(+ 25%)	$19620
Heart failure in Met+DPP-4i	0.013(−25%)	$19120
Heart failure in Met+DPP-4i	0.021(+ 25%)	$19880
Stroke in Met+DPP-4i	0.002(−25%)	$19470
Stroke in Met+DPP-4i	0.003(+ 25%)	$19520
Heart failure in Met+SU	0.015(−25%)	$19790
Heart failure in Met+SU	0.025(+ 25%)	$19210
Stroke in Met+SU	0.015(−25%)	$19660
Stroke in Met+SU	0.025(+ 25%)	$19340
Costs of myocardial infarction	$13970(−25%)	$19430
Costs of myocardial infarction	$23284(+ 25%)	$19370
Costs of heart failure	$10589(−25%)	$19450
Costs of heart failure	$17648(+ 25%)	$19550
Costs of stroke	$15954(−25%)	$19660
Costs of stroke	$9924(+ 25%)	$19340
Costs of severe hypoglycemia	$110(−25%)	$19500
Costs of severe hypoglycemia	$183(+ 25%)	$19500
Costs of weight gain	$217(−25%)	$19520
Costs of weight gain	$361(+ 25%)	$19470

Table 7 Results of one-way sensitivity analyses for base-case scenario *(Continued)*

	Values	Estimated ICER
Costs of insulin glargine	$29171(−20%)	$20320
Costs of insulin glargine	$4375(+ 20%)	$18680
Death rate	0.019 (age 60–70) / 0.046 (age 71–80) / 0.096 (age 81–85) (−10%)	$20780
Death rate	0.024 (age 60–70) / 0.057 (age 71–80) / 0.118 (age 81–85) (+ 10%)	$18470
Time horizon	20 years (− 20%)	$24250
Time horizon	30 years (+ 20%)	$17580
Same cardiovascular event rates from 2 years after dual therapy	MI, 0.004 / HF, 0.02 / Stroke, 0.02	$20420
Age at start of metformin monotherapy	55 (−8%)	$21360
Age at start of metformin monotherapy	65 (+ 8%)	$18120

Acronyms: SU-sulfonylurea, DPP-4i-dipeptidyl peptidase-4 inhibitor, Met; metformin, MI-myocardial infarction, HF-heart failure

would enter the market in a 10 year-time frame and that generic DPP-4i prices would be 16% of the corresponding brand name drug price. Nevertheless, prices of generic drugs are set up as 94% of brand name drug prices when there is only one generic competitor in the market [32]. A decrease in the price of generic drugs to 16% of the price of brand name drugs is observed only when there are several generic competitors in the market. Therefore, Bergenheim et al., (2012) may underestimate DPP-4i generic drug prices.

Zhang et al., (2014) compared metformin+SU, metformin+DPP-4i, metformin+GLP-1 receptor agonists, and insulin as the second-line therapy using a Markov model with 10 A1c states [8]. Zhang et al., (2014) only assessed the medication cost; Authors did not include the costs of medical events related with diabetic complications. Zhang et al., (2014) did not include either in the analysis the costs associated with severe hypoglycemia. Furthermore, they assumed that the termination state was either the first diabetes-related complication or death.

Table 8 Probabilistic Sensitivity Analysis

Second-line agent add-on to Metformin	Average Total		Average Incremental		
	Costs	Life Years Gained	Costs	Life Years Gained	ICER
Sulfonylurea	$7004 (±316.52)	11.93 (±0.07)			
Dipeptidyl peptidase-4 inhibitor	$18790 (±1008.70)	12.52 (±0.07)	$ 11786 (±976.92)	0.59 (±0.02)	$19980

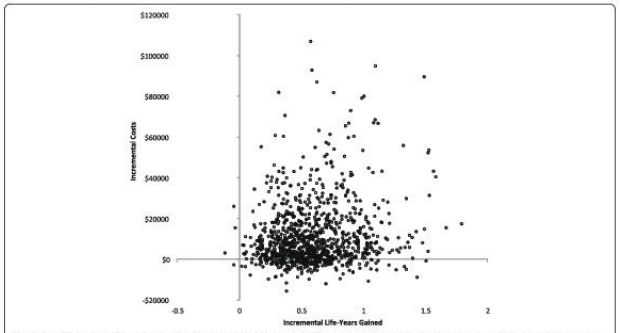

Fig. 3 Cost-Effectiveness Plane, Scatter plots showing the 1000 cases of differences in costs and in the life-year gained from the trial data using 1000 bootstrap replicates

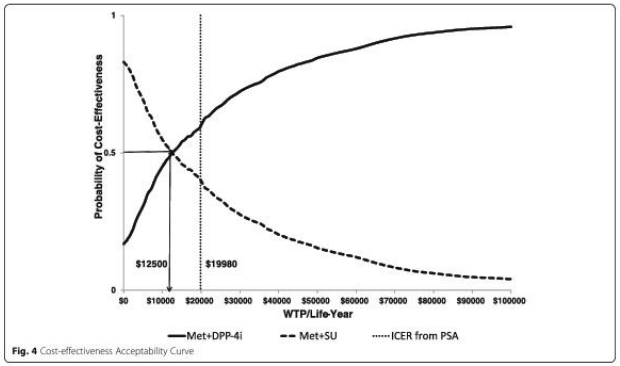

Fig. 4 Cost-effectiveness Acceptability Curve

Zhang et al., (2014) set up three different A1c goals (i.e., 6.5, 7, and 8%) to evaluate the impact of glycemic control goals on patients with diabetes. Like in our study, they considered insulin triple therapy after dual therapy failure, but they assumed that patients initiated insulin therapy only after exceeding the A1c goals. This assumption lead to the initiation of insulin therapy only after 1.59 to 2.76 years after onset T2D diagnosis. Nevertheless, assuming that insulin initiation is based on patients' A1c levels may lead to overestimate insulin initiating rate due to well document barriers for the patient's and provider's to start insulin therapy [33–35]. In addition, the timeline for second line therapy before insulin therapy may not be long enough to show clinically meaningful differences in outcomes associated with the use of alternative second line therapies. Last, Zhang et al., (2014) assumed that the first diabetes-related complication and death were termination states, resulting in lower rates of diabetic complications and costs than this study estimations. Zhang et al., (2014) concluded that the life-years and QALYs until the first event were similar in the four treatment pathways and that metformin+SU had similar outcomes and lower drug costs compared to the assessed treatment alternatives.

Limitations

The Markov model used in this study does not intent to represent the actual clinical progression of patients with diabetes but to assess differences in two alternative therapy pathways under a defined set of assumptions. Thus, study results should be interpreted taking into consideration some limitations. Adult patients may develop T2D at any time during their life. This study assumed patients entered the model at age 60 years old. Study results are not generalizable to other T2D therapy initiation ages.

The Markov model employed in this study, assessed alternative pharmacological treatment pathways for T2D. To define the Markov states, this study model included most common drug therapies for the treatment of T2D instead of conventional health states, such as patient' A1c level or disease progress status [36, 37]. Therefore, in this study transition probabilities did not depend on changes in A1c or disease progressions but on treatment failure rates observed in prior studies in patients with T2D.

We set the study time horizon at 25 years for the base-case because the survival data were available only until patients reach 85-years old. The death hazard ratio was estimated based on data drawn from a two-year trial results. Therefore, a more robust model would include death rates data for patients with diabetes for a longer time horizon [38].

Due to scarcity of studies some clinical input data were derived from trials outside of the US. Treatment failure rates for metformin were derived from studies conducted in the US, Canada, and the European Union (EU). Death hazard ratio for metformin+SU was derived from a study conducted in the United Kingdom and cardiovascular complication rates for dual therapy were derived from the studies conducted in the EU. Hypoglycemia data were derived from an international randomized clinical trial. Hypoglycemic events might lead to changes in medication. Future studies may include more treatment alternatives to account for changes in medication. Representativeness of study results may improve in the future using ongoing long-term comparative effectiveness studies conducted in the US in patients with T2D as model inputs [39]. Additionally, the study did not account for changes in clinical practice that have occurred after the publication of some of the studies used to derive the clinical input data.

Probabilities of treatment failure, hypoglycemia and cardiovascular complications were derived from studies with a limited time horizon. In addition, we assumed that the rates of cardiovascular events and treatment failure, and insulin dose remained constant through the study time horizon. Hypoglycemia rate data were derived from a trial which included patients with prediabetes. Thus, the hypoglycemia rate may be overestimated.

Cost-effectiveness estimations included only hypoglycemia, weight gain and cardiovascular events-related costs. While these outcomes have been documented as the main outcomes differences between DPP-4i and SU other differences in outcomes between these treatment alternatives may exist [9, 40]. Weight gain caused by insulin glargine was not considered in this study. Including different weight gain rates for each treatment pathway would yield more robust estimations but it would significantly increase the complexity of the Markov model. We conducted a sensitivity analysis for several key study measures including weight gain rates and study results did not change significantly. Microvascular complications, such as amputation, blindness or end state renal disease were not included either in the study because these outcomes are associated with uncontrolled blood glucose level and not with the use of specific drugs. Acute treatment costs for cardiovascular events were included in the CEA. Thus, medical costs for T2D related cardiovascular events could be underestimated.

We assumed that patients were adherent to antidiabetic medications when estimating the outcomes and drug costs. High medication costs may impact on the DPP-4i treatment adherence. Likewise, the risk of hypoglycemia may impact on the adherence of SU and insulin. Fixed-dose combination drugs were not considered when estimating medication costs. Self-monitoring of blood glucose related costs were not included in the CEA.

This study assessed metformin+SU and metformin +DPP-4i treatment pathways; other treatment alternatives are marketed in the US such as newly FDA approved sodium glucose cotransporter-2 inhibitors and GLP-1 receptor agonists. Last, study model did not include triple oral or dual oral plus non-insulin injectable treatment alternatives before initiating insulin and prandial insulin option. Future studies may include more complex Markov models to compare the cost-effectiveness of all currently available T2D treatment pathways. Future studies might consider the use of quality of life adjusted years as the study outcomes.

In spite of these limitations, this study has important strengths. Our study assessed three alternative treatment pathways during a long-term time horizon to better capture progression of the disease overtime. In addition, this study comprehensively assessed all prescription drug and health care costs related with diabetes complications. Furthermore, this study used insulin initiating rate to reflect both patients and providers decision making process to start insulin therapy.

Conclusions

This study assessed the cost-effectiveness of most commonly recommended in clinical guidelines T2D alternative long-term treatment pathways. The treatment pathway with DPP-4i as the second-line therapy was cost-effective compared to SU from the US health care payer perspective. The results of the one way and probabilistic sensitive analyses indicate that study findings are not sensitive to changes in the parameters used in the model. More studies assessing the cost-effectiveness of all long-term alternative T2D treatment pathways marketed in the US are needed.

Abbreviations

A1c: Glycated hemoglobin; AWP: Average wholesale price; CEA: Cost-effectiveness analysis; CEAC: Cost-effectiveness acceptability curve; CPI: Consumer price index; DDD: Defined daily dose; EU: European union; FDA: U.S. Food and drug administration; ICER: Incremental cost-effectiveness ratio; NADAC: National average drug acquisition cost; OAD: Oral antidiabetic drugs; T2D: Type 2 diabetes; US: United States; WHO: World Health Organization; WTP: Willingness to pay

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Availability of data and materials

This study used data readily available in the literature. Study data are available upon request.

Authors' contributions

ES conceived the idea of conducting this study, designed the study, contributed to the data collection, analyzed and interpreted data, and drafted the manuscript. CSK collaborated in the data collection, analysis and

interpretation of study results and drafted some sections of the manuscript. CSK worked under the supervision of ES. RRM collaborated in the conceptualization and design of the study, interpreted the data, and drafted the manuscript. ES and RRM are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

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Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable. This study does not contain any individual person's identifiable data or information.

Competing interests

The authors declare that they have no competing interests.

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ANALISIS EFEKTIVITAS BIAYA PENGGUNAAN TERAPI KOMBINASI INSULIN DAN OHO PADA PASIEN DIABETES MELITUS TIPE 2 RAWAT JALAN DI RSUD WANGAYA

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ABSTRAK

Bervariasinya penggunaan terapi insulin tunggal atau kombinasi insulin dengan Obat Hipoglikemik Oral (OHO) pada pasien DM tipe 2 dengan kontrol glukosa darah yang belum adekuat akan mengakibatkan adanya perbedaan dalam biaya dan efektivitas terapinya. Perlu dilakukan penelitian yang ditujukan untuk mengetahui jenis terapi mana yang memberikan total biaya medis langsung yang lebih rendah dan efektivitas yang lebih tinggi pada pasien DM tipe 2 rawat jalan di RSUD Wangaya.

Penelitian ini merupakan penelitian deskriptif yang dilakukan secara prospektif dan studi follow up dari bulan Maret sampai dengan Juni 2012. Subyek penelitian adalah 70 pasien DM tipe 2 yang memenuhi kriteria inklusi dan yang tidak memenuhi kriteria eksklusi. Data dianalisis untuk mengetahui jenis terapi dan biaya medis langsung. Efektivitas terapi dinilai dari tercapainya target HbA1c <7% setelah follow up 3 bulan terapi dan tidak munculnya efek samping obat (hipoglikemia). Metode ACER dan ICER digunakan untuk menganalisa jenis terapi insulin yang paling cost-effective.

Hasil penelitian menunjukkan jenis terapi insulin tunggal atau kombinasi insulin dengan OHO yang digunakan untuk pasien DM tipe 2 beserta total biaya medis langsung tiap bulannya yaitu, insulin aspart (Rp 417.861,00), insulin detemir (Rp 316.672,00), kombinasi insulin aspart dengan metformin (Rp 430.371,00), kombinasi insulin detemir dengan metformin (Rp 329.182,00), kombinasi insulin glargin dengan metformin (Rp 329.182,00), dan kombinasi insulin glargin dengan metformin (Rp 435,652.00). Berdasarkan perhitungan ACER dan ICER, terapi insulin yang paling cost-effective adalah kombinasi insulin aspart dengan metformin.

Kata kunci : Analisis efektivitas biaya, DM tipe 2, Insulin, OHO

1. PENDAHULUAN

Diabetes melitus merupakan salah satu penyakit yang telah menjadi masalah kesehatan dunia. Badan Kesehatan Dunia (World Health Organization/WHO) memperkirakan jumlah penderita diabetes melitus (DM) di Indonesia akan meningkat hingga dua sampai tiga kali lipat pada tahun 2030 dari 8,4 juta mencapai 21,3 juta orang (Perkumpulan Endokrinologi Indonesia, 2011).

Upaya terapi non farmakologi dan farmakologi telah dilakukan untuk meningkatkan kualitas hidup pasien diabetes melitus. Terapi farmakologi untuk diabetes melitus (DM) tipe 2 meliputi OHO dan terapi insulin. Insulin diberikan untuk pasien yang memiliki nilai HbA1c ≥7,5% dengan kadar glukosa darah puasa >250 mg/dL atau pasien yang gagal dengan terapi OHO (Obat Hipoglikemik Oral) (American Diabetes Association, 2011). Penggunaan insulin dapat dikombinasikan dengan OHO apabila kadar glukosa darah tidak terkontrol dengan baik (HbA1c >9%) dalam jangka waktu tiga bulan dengan dua OHO (Perkumpulan Endokrinologi Indonesia, 2011).

Terapi obat pada pasien diabetes melitus dilakukan seumur hidup sehingga membutuhkan biaya yang sangat besar. Misalnya, di Amerika pada tahun 2007 mencapai total biaya sebesar $174 juta yang meliputi $116 juta biaya medis langsung dan $58 juta biaya medis tidak langsung (Centers for Disease Control, 2011).

Bervariasinya penggunaan terapi obat erapi insulin tunggal atau kombinasi insulin engan OHO) akan mengakibatkan adanya erbedaan dalam biaya dan luaran terapinya ehingga diperlukan analisis efektivitas biaya enggunaan terapi insulin tunggal serta ombinasi insulin dengan OHO untuk engetahui penggunaan terapi insulin yang aling cost-effective.

. METODE PENELITIAN

.1. Desain Penelitian

Penelitian yang dilaksanakan merupakan enelitian deskriptif yang dilakukan secara rospektif dan studi follow up selama 3 bulan rhadap pasien DM tipe 2 rawat jalan RSUD Vangaya yang dilaksanakan dari bulan Maret ampai dengan Juni 2012.

.2. Bahan dan Alat Penelitian

Bahan yang digunakan adalah data kartu ekam medis pasien, perincian biaya obat, dan witansi pasien DM tipe 2 rawat jalan RSUD Vangaya. Alat yang digunakan dalam penelitian ni adalah lembar pengumpulan data.

.3. Prosedur Penelitian

.3.1. Pemilihan Subyek Penelitian

Subyek penelitian adalah 70 pasien DM pe 2 yang melakukan rawat jalan di RSUD Vangaya yang telah memenuhi kriteria inklusi an tidak memenuhi kriteria eksklusi.

riteria inklusi :

a. Pasien berumur 40-60 tahun.
b. Pasien dengan DM tipe 2 dengan kadar GDP (Glukosa Darah Puasa) 250 mg/dL – 350 mg/dL..
c. Pasien yang sedang melakukan kontrol ketika penelitian dilakukan.
d. Pasien yang bersedia menjadi responden.
e. Pasien yang mendapat terapi insulin tunggal atau terapi kombinasi insulin dengan OHO.

riteria eksklusi :

a. Pasien dengan data rekam medis yang tidak lengkap.
b. Pasien DM tipe 2 yang sedang hamil.
c. Pasien yang menggunakan kontrasepsi dan obat-obat lainnya yang dapat mempengaruhi kadar gula darah pasien seperti loop diuretik, tiazid, dan kortison.
d. Pasien yang merokok.
e. Pasien DM tipe 2 dengan penyakit penyerta.

2.3.2. Pengumpulan Data

Data dikumpulkan dari rekam medis pasien mengenai nama, umur, jenis obat, kadar GDP, kadar GD2JPP (Glukosa Darah 2 Jam Post Puasa), dan kadar GDS (Glukosa Darah Sewaktu). Dicatat data laboratorium mengenai kadar GDP, GD2JPP, dan GDS hasil pemeriksaan laboratorium setelah 3 bulan follow up penggunaan terapi insulin tunggal dan kombinasi terapi insulin dengan OHO. Data mengenai biaya obat dan biaya administrasi diperoleh dari instalasi farmasi/apotek dan bagian keuangan RSUD Wangaya. Selain itu dilakukan wawancara sebagai pendukung untuk menyempurnakan data yang berasal dari metode dokumentasi. Wawancara dilakukan secara langsung kepada subyek penelitian mengenai data alamat, nomor telepon, dan muncul tidaknya efek samping yaitu hipoglikemia dengan gejala seperti rasa lemah, gemetar, pusing, dan keluar keringat dingin selama terapi berlangsung.

2.3.3. Analisis Data

Analisis data dilakukan dengan sudut pandang institusi (rumah sakit), yang meliputi:

A. Demografi Subyek Penelitian

Karakteristik pasien meliputi gambaran distribusi berdasarkan jenis kelamin, umur, serta kadar HbA1c.

B. Gambaran Jenis Terapi

Analisis data dilakukan dengan merangkum data distribusi jenis obat berdasarkan pemakaian terapi insulin tunggal dan terapi kombinasi insulin dengan OHO yang diresepkan pada subyek penelitian.

C. Perhitungan Biaya Medis Langsung

Perhitungan total biaya medis langsung tiap bulannya yang meliputi biaya obat, biaya pemeriksaan dokter, biaya laboratorium, dan biaya administrasi. Total biaya obat diperoleh dengan menjumlahkan biaya obat dari bulan Maret sampai dengan bulan Mei sedangkan total biaya konsultasi dan pemeriksaan dokter, biaya laboratorium serta biaya administrasi diperoleh dari pengeluaran biaya tersebut selama bulan Maret sampai dengan Juni. Total biaya medis langsung yang dikeluarkan subyek penelitian tiap bulannya diperoleh dengan menjumlahkan rata-rata total biaya obat dengan rata-rata penjumlahan total biaya pemeriksaan dan

konsultasi dokter, biaya laboratorium, dan biaya administrasi.

D. Penilaian Efektivitas Terapi

Efektivitas terapi penggunaan terapi insulin tunggal dan kombinasi insulin dengan OHO yang diresepkan dilihat dari pencapai target terapi HbA1c <7% setelah 3 bulan follow up dan tidak munculnya efek samping obat yaitu hipoglikemia pada subyek penelitian.

E. Perhitungan Efektivitas Biaya Terapi

Analisa efektivitas biaya dengan metode Average Cost Effectiveness Ratio (ACER) dan Incremental Cost Effectiveness Ratio (ICER). Cost-effective dengan ACER dihitung berdasarkan perhitungan total biaya medis langsung dibagi dengan efektivitas terapi sedangkan berdasarkan ICER, cost-effective dihitung dengan melihat rasio perbedaan biaya antara dua alternatif terhadap perbedaan dalam efektivitas antara keduanya.

3. HASIL DAN PEMBAHASAN

3.1. Demografi Subyek Penelitian

Data demografi subyek penelitian meliputi data demografi berdasarkan jenis kelamin, usia, dan kadar HbA1c. Pouwer et al (2010) menyatakan bahwa perbedaan jenis kelamin dan stres emosional akan berhubungan dengan peningkatan risiko terjadinya penyakit DM tipe 2. Hasil penelitian tersebut menunjukkan bahwa prevalensi terjadinya DM tipe 2 lebih tinggi pada pria dengan peningkatan stres emosional.

Berdasarkan usia, hasil penelitian menunjukkan bahwa penderita DM tipe 2 lebih banyak terjadi pada usia di atas 45 tahun. Usia di atas 45 tahun lebih mudah menderita DM tipe 2 dikarenakan dengan bertambahnya usia maka akan terjadi penurunan aktivitas fisik. Penurunan aktivitas fisik dapat mengakibatkan terjadinya abnormalitas metabolisme glukosa yang nantinya akan mempengaruhi induksi glukosa terhadap sekresi insulin dan resistensi insulin (Meneilly, 2010). Halter dan Annete (2003) menyatakan bahwa dengan pertambahan usia maka akan terjadi penurunan sensitivitas sel beta pankreas terhadap hormon inkretin dan resistensi insulin akibat rusaknya sel beta pankreas yang menyebabkan terjadinya perkembangan DM tipe 2.

Perkumpulan Endokrinologi Indonesia (2011) menyebutkan bahwa pasien dengan HbA1c >9% mulai mendapatkan terapi insulin monoterapi atau kombinasi insulin dengan OHO. Pada penelitian ini diketahui bahwa 100% subyek penelitian memiliki kadar HbA1c lebih dari 9% sehingga pemberian terapi insulin baik tunggal maupun kombinasi insulin dengan OHO memang tepat diberikan pada pasien. Data demografi subyek penelitian selengkapnya dapat dilihat pada Tabel A.1.

3.2. Penggunaan Terapi Insulin Pada Pasien DM Tipe 2

Terapi farmakologi untuk pasien DM tipe 2 dapat menggunakan OHO dan insulin. Pemberian terapi insulin pada pasien dengan HbA1c >9% dapat diberikan dengan monoterapi (insulin tunggal) atau kombinasi antara insulin dengan OHO (Perkumpulan Endokrinologi Indonesia, 2011). Penggunaan insulin tunggal lebih sedikit dibandingkan kombinasi insulin dengan OHO. Penggunaan insulin kerja cepat (insulin aspart) lebih banyak digunakan baik secara tunggal maupun kombinasi dibandingkan penggunaan insulin kerja panjang (insulin detemir). Penelitian Bretzel et al (2006) menunjukkan bahwa insulin kerja cepat (insulin aspart) memiliki kelebihan dalam memperbaiki nilai HbA1c, baik dalam mengontrol glukosa darah post-prandial, dan angka terjadinya hipoglikemia lebih sedikit jika dibandingkan dengan penggunaan insulin kerja panjang (insulin detemir) selama 6 bulan penelitian. Jenis terapi insulin yang digunakan dapat dilihat pada Tabel A.2.

3.3. Analisis Efektivitas Biaya

3.3.1. Total Biaya Medis Langsung

Total biaya medis langsung tiap bulan adalah hasil penjumlahan rata-rata biaya obat selama 3 bulan follow up terapi dengan rata-rata biaya penjumlahan biaya laboratorium, biaya pemeriksaan dan konsultasi, serta biaya administrasi selama bulan Maret sampai bulan Juni. Tabel A.3. menunjukkan bahwa total biaya medis langsung untuk penggunaan kombinasi insulin glargin dengan akarbose paling tinggi, yaitu sebesar Rp 435.652,00, lebih tinggi Rp 5.281,00 terhadap total biaya medis langsung penggunaan kombinasi insulin aspart dengan metformin. Total biaya medis langsung terkecil dimiliki oleh penggunaan tunggal insulin detemir, yaitu sebesar Rp 316.672,00. Akibat biaya administrasi, biaya laboratorium, serta biaya pemeriksaan dan konsultasi dokter tiap pasien sama, maka besar kecilnya total biaya medis langsung yang dikeluarkan tiap bulan ditentukan oleh besarnya biaya obat. Semakin

besar biaya obat maka semakin tinggi pula biaya total medis langsungnya.

3.3.2. Efektivitas terapi

Pada penelitian ini efektivitas terapi dilihat dari tidak munculnya efek samping obat dan pencapaian target terapi. Efek samping akibat penggunaan terapi insulin salah satunya yaitu hipoglikemia. Selama follow up 3 bulan terhadap rekam medis pasien dan hasil wawancara diketahui bahwa tidak ada efek samping obat (hipoglikemia) yang muncul pada subyek penelitian. Pencapaian target terapi dilihat dari pencapaian target HbA1c <7% setelah 3 bulan follow up terapi.

Penggunaan terapi insulin baik insulin aspart maupun insulin detemir menunjukkan efektivitas terapi yang lebih rendah apabila diberikan secara tunggal dibandingkan apabila kedua jenis terapi insulin ini dikombinasikan dengan OHO. Pada penelitian ini kombinasi insulin aspart dengan metformin menunjukkan efektivitas terapi tertinggi (54,16%). Penggunaan kombinasi insulin aspart dengan metformin memberikan keuntungan dalam pengontrolan glukosa darah. Metformin bertindak sebagai insulin sensitizer terutama dengan meningkatkan respon hati terhadap insulin dan dapat mengontrol produksi glukosa hepatik ketika puasa. Apabila metformin dikombinasikan dengan insulin aspart akan memberikan keuntungan dalam menurunkan kadar glukosa darah dimana insulin aspart mampu dalam mengontrol glukosa post-prandial sedangkan metformin mengontrol glukosa darah ketika puasa sehingga kadar glukosa darah tetap terkontrol setiap waktu (Riddle, 2008).

3.3.3. Perhitungan Efektivitas Biaya Berdasarkan ACER

Penilaian analisis efektivitas biaya menggunakan metode ACER bertujuan untuk membandingkan total biaya suatu program atau alternatif pengobatan dibagi dengan keluaran klinis untuk menghasilkan perbandingan yang mewakili biaya tiap hasil klinis yang spesifik, independen dari pembanding.

Hasil perhitungan ACER (Tabel A.4.) menunjukkan bahwa pilihan terapi yang paling cost-effective adalah penggunaan terapi kombinasi insulin aspart dengan metformin dengan nilai ACER paling rendah yaitu Rp 7.946,00 per % efektivitas terapi. Penggunaan terapi insulin glargin dengan metformin menunjukkan pengobatan yang paling tidak cost-effective dilihat nilai ACER yang diperoleh paling tinggi.

3.3.4. Perhitungan Efektivitas Biaya Berdasarkan ICER

ICER didefinisikan sebagai rasio perbedaan biaya antara dua alternatif terhadap perbedaan dalam efektivitas antara keduanya (Skrepnek, 2005). Pada perhitungan ICER, data total biaya medis langsung dan efektivitas terapi diurutkan dalam suatu tabel dan penyusunan pada tabel berdasarkan nilai efektivitas terapi yaitu diurutkan dari efektivitas terapi terkecil hingga efektivitas terapi terbesar (Bala et al., 2002).

Hasil perhitungan ICER yang pertama ditunjukkan pada Tabel A.5. Jenis terapi diurutkan berdasarkan tingkat efektivitas terapinya dari jenis terapi yang memiliki efektivitas terendah ke efektivitas tertinggi. Selanjutnya dilakukan eliminasi. Hasil eliminasi tahap I perhitungan ICER dapat dilihat pada

Setelah eliminasi tahap I, perhitungan ICER diulang kembali dengan tetap mengurutkan jenis terapi berdasarkan tingkat efektivitasnya. Proses eliminasi dilakukan kembali dengan melihat terapi yang bersifat strict dominance. Terapi kombinasi insulin detemir dan aspart menunjukkan adanya penurunan biaya dan peningkatan efektivitas dibandingkan dengan terapi insulin detemir dan terapi insulin aspart sehingga kedua jenis terapi ini (insulin detemir dan insulin aspart) dieliminasi dari perhitungan ICER. Hasil

Pada ICER, suatu intervensi dieliminasi apabila interversi tersebut termasuk ke dalam dua kategori, yaitu strict dominance dan extended dominance. Jenis eliminasi yang digunakan pada penelitian ini adalah dengan menerapkan eliminasi intervensi yang bersifat strict dominance. Suatu intervensi dikatakan strict dominance apabila ada interversi lain yang memiliki biaya yang lebih rendah dan efektivitas yang lebih tinggi (Bala et al., 2002).

Tabel A.6. Jenis terapi yang dieliminasi pada tahap I adalah kombinasi insulin glargin dan metformin. Hal ini dikarenakan kombinasi insulin glargin dan metformin bersifat strict dominance yaitu biaya yang dibutuhkan lebih mahal dan kurang efektif jika dibandingkan dengan penggunaan insulin detemir tunggal.

eliminasi tahap II perhitungan ulang ICER dapat dilihat pada Tabel A.7.

Hasil eliminasi tahap II menyisakan 3 jenis terapi dimana ketika dilakukan perhitungan ulang ICER. Berdasarkan hasil perhitungan kembali nilai ICER, nilai ICER kombinasi insulin aspart dan metformin merupakan nilai ICER terendah. Intervensi paling cost-effective dilihat dari nilai ICER terendah (Phillips, 2009).

Perhitungan analisa efektivitas biaya menggunakan ICER dilakukan untuk memberikan beberapa pilihan altenatif yang dapat diterapkan di masyarakat. Pemilihan alternatif jenis perawatan dapat disesuaikan dengan pertimbangan dana atau tersedia tidaknya jenis alternatif tersebut. Apabila tersedia dana sebesar Rp 430.371,00 atau lebih, maka terapi kombinasi insulin aspart dengan metformin dapat diterapkan dan pasien akan mendapatkan jenis terapi yang paling cost-effective dibandingkan dua alternatif terapi yang lain. Penggunaan kombinasi insulin aspart dan metformin memberikan selisih penurunan harga sebesar Rp 1.296,00 untuk setiap selisih penambahan 1% efektifitas dibandingkan dengan kombinasi alternatif sebelumnya. Namun, apabila sumber dana yang tersedia kurang dari Rp 430.371,00 maka pasien akan mendapatkan alternatif terapi cost-effective lainnya yaitu terapi kombinasi insulin detemir dengan mertformin. Perhitungan ICER juga memberikan alternatif terapi yang dinilai cost-effective yang dapat dipilih untuk disesuaikan dengan kondisi klinis pasien.

4. KESIMPULAN

Jenis terapi insulin baik tunggal maupun kombinasi dengan OHO yang digunakan pada pasien DM tipe 2 rawat jalan di RSUD Wangaya beserta total biaya medis langsung yang dikeluarkan tiap bulannya meliputi insulin tunggal aspart sebesar Rp 417.861,00 dan untuk insulin tunggal detemir sebesar Rp 316.672,00. Penggunaan kombinasi insulin dengan OHO adalah sebagai berikut: kombinasi insulin aspart dengan metformin sebesar Rp 430.371,00, kombinasi insulin detemir dengan metformin sebesar Rp 329.182,00, kombinasi insuin glargin dengan metformin sebesar Rp 329.182,00, dan kombinasi glargin dengan akarbose sebesar Rp 435.652,00. Terapi insulin yang paling cost-effective berdasarkan ACER dan ICER adalah kombinasi insulin aspart dengan metformin.

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APENDIKS A.

Tabel A.1. Data demografi subyek penelitian

Kriteria	Jumlah (orang)	Persentase (%)
Jenis kelamin		
Pria	48	68,57
Wanita	22	31,43
Umur		
<45 tahun	7	10,00
>45 tahun	63	90,00
HbAIc		
<9 %	0	0
>9 %	70	100,00

Tabel A.2. Jenis terapi insulin yang diperoleh subyek penelitian

Golongan Obat	Jenis Obat		Jumlah Responden	Persentase (%)
Insulin tunggal				
Insulin kerja cepat	Insulin aspart	Novorapid® FlexPen®	12	17,14
Insulin kerja panjang	Insulin detemir	Levemir® FlexPen®	4	5,71
Kombinasi				
Insulin kerja cepat dan Biguanid	Insulin aspart + Metformin	Novorapid® FlexPen® + metformin	24	34,28
Insulin kerja panjang dan Biguanid	Insulin detemir + Metformin	Levemir® FlexPen® + metformin	15	21,44
	Insulin glargin + metformin	Lantus® FlexPen® + metformin	9	12,86
Insulin kerja panjang dan penghambat glukosidase alfa	Insulin glargin + Akarbose	Lantus® FlexPen® + glucobay®	6	8,57
Total			70	100,00

Tabel A.3. Biaya medis langsung penggunaan insulin tunggal dan kombinasi insulin dengan OHO selama 4 bulan penelitian

Jenis Obat	B1 (Rp)	R1 (Rp)	B2 (Rp)	B3 (Rp)	B4 (Rp)	B2+B3+ B4 (Rp)	R2 (Rp)	T (Rp)
Insulin aspart	1.055.583	351.861	192.000	64.000	8.000	264.000	66.000	417.861
Insulin detemir	752.016	250.672	192.000	64.000	8.000	264.000	66.000	316.672
Insulin aspart Metformin	1.093.113	364.371	192.000	64.000	8.000	264.000	66.000	430.371
Insulin detemir Metformin	789.546	263.182	192.000	64.000	8.000	264.000	66.000	329.182
Insulin glargin Metformin	789.546	263.182	192.000	64.000	8.000	264.000	66.000	329.182
Insulin glargin Akarbose	1.108.956	369.652	192.000	64.000	8.000	264.000	66.000	435.652

Ket. tabel: B1 (biaya obat selama 3 kali terapi); B2 (biaya laboratorium); B3 (biaya pemeriksaan dokter dan konsultasi); B4 (biaya administrasi); R1 (rata-rata biaya obat); R2 (rata-rata penjumlahan dari (B2 + B3 + B4)); T (total biaya medis langsung tiap bulannya (R1+R2))

Tabel A.4. Hasil perhitungan ACER berdasarkan total biaya medis langsung tiap bulan

No	Jenis Terapi	Total Biaya Medis Langsung (Rp)	Efektivitas Terapi (%)	ACER (Rp/% efektivitas)
1	Insulin aspart	417.861	33,33	12.537
2	Insulin detemir	316.672	25,00	12.667
3	Insulin aspart + metformin	430.371	54,16	7.946
4	Insulin detemir + metformin	329.182	40,00	8.230
5	Insulin glargin + metformin	329.182	22,22	14.815
6	Insulin glargin + akarbose	435.652	50,00	8.713

Tabel A.5. Hasil perhitungan ICER penggunaan insulin tunggal dan kombinasi insulin dengan OHO

No	Jenis Terapi	C (Rp)	E (%)	ΔC (Rp)	ΔE (%)	ICER (Rp / % efektivitas)
1	Insulin glargin + metformin	329.182	22,22	329.182	22,22	14.815
2	Insulin detemir	316.672	25,00	-12.510	2,78	-4.500
3	Insulin aspart	417.861	33,33	101.189	8,33	12.148
4	Insulin detemir + metformin	329.182	40,00	-88.679	6,67	-13.295
5	Insulin glargin + akarbose	435.652	50,00	106.470	10,00	10.647
6	Insulin aspart + metformin	430.371	54,16	-5.281	4,16	-1.269

Ket. tabel: C (total biaya medis langsung tiap bulan); E (efektivitas); ΔC (perbedaan biaya); ΔE (perbedaan efektivitas)

Tabel A.6. Hasil eliminasi tahap I perhitungan ICER

No	Jenis Terapi	C (Rp)	E (%)	ΔC (Rp)	ΔE (%)	ICER (Rp / % efektivitas)
1	Insulin detemir	316.672	25,00	316.672	25,00	12.667
2	Insulin aspart	417.861	33,33	101.189	8,33	12.148
3	Insulin detemir + metformin	329.182	40,00	-88.679	6,67	-13.295
4	Insulin glargin + akarbose	435.652	50,00	106.470	10,00	10.647
5	Insulin aspart + metformin	430.371	54,16	-5.281	4,16	-1.269

Ket. tabel: C (total biaya medis langsung tiap bulan); E (efektivitas); ΔC (perbedaan biaya); ΔE (perbedaan efektivitas)

Tabel A.7. Hasil eliminasi tahap II perhitungan ICER

No	Jenis Terapi	C (Rp)	E (%)	ΔC (Rp)	ΔE (%)	ICER (Rp / % efektivitas)
1	Insulin detemir + metformin	329.182	40,00	329.182	40,00	8.230
2	Insulin glargin + akarbose	435.652	50,00	106.470	10,00	10.647
3	Insulin aspart + metformin	430.371	54,16	-5.281	4,16	-1.269

Ket. tabel: C (total biaya medis langsung tiap bulan); E (efektivitas); ΔC (perbedaan biaya); ΔE (perbedaan efektivitas)

ANALISIS EFEKTIVITAS BIAYA PENGGUNAAN TERAPI INSULIN DAN INSULIN KOMBINASI PADA PASIEN DIABETES MELLITUS TIPE II RAWAT JALAN DI RSUP SANGLAH

ANALYSIS OF COST EFFECTIVENESS USE OF INSULIN THERAPY AND INSULIN COMBINATION ON DIABETES MELLITUS TYPE II OUTPATIENTS IN RSUP SANGLAH

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Abstrak: Diabetes mellitus (DM) tipe 2 merupakan suatu kelompok penyakit metabolik dengan karakteristik hiperglikemia yang terjadi karena resistensi insulin disertai defisiensi insulin relatif. Bervariasinya penggunaan terapi insulin tunggal atau kombinasi insulin dengan antidiabetik oral pada pasien DM tipe 2 dengan kontrol glukosa darah yang belum adekuat akan mengakibatkan adanya perbedaan dalam biaya dan efektivitas terapinya. Penelitian ini merupakan penelitian deskriptif yang dilakukan secara prospektif dan studi *follow up* dari bulan Mei sampai dengan Agustus 2017. Subyek penelitian adalah 70 pasien DM tipe 2 yang memenuhi kriteria inklusi. Data dianalisis untuk mengetahui jenis terapi dan biaya medis langsung. Efektivitas terapi dinilai dari tercapainya target HbA1c <7% setelah *follow up* 3 bulan terapi dan tidak munculnya efek samping obat (hipoglikemia). Metode ACER digunakan untuk menganalisa jenis terapi insulin yang paling *cost-effective*. Berdasarkan data yang didapatkan dari rekam medis RSUP Sanglah Denpasar, jumlah pasien DM tipe 2 lebih banyak diderita oleh laki-laki yaitu 47 orang dengan presentase 67,14%, umur >45 tahun yaitu 63 orang dengan presentase 90,00%. Jumlah pasien DM tipe 2 yang mencapai target GDP yaitu 34 orang dengan presentase 48,57%, mencapai target HbA1C yaitu 60 orang dengan presentase 85%. Jumlah pasien DM tipe 2 lebih banyak yang menggunakan terapi kombinasi insulin aspart dengan insulin glargine yaitu 42 orang dengan presentase 60%. Total biaya medis langsung yang menunjukkan jumlah paling murah adalah penggunaan terapi insulin glargine dengan metformin yaitu Rp. 274.880,00. Efektivitas terapi yang lebih besar ditunjukkan oleh jenis terapi kombinasi insulin glargine dengan metformin yaitu 63,63%. Efektivitas biaya yang lebih rendah ditunjukkan oleh jenis terapi kombinasi insulin glargine dengan metformin yaitu Rp. 4,32 persentase efektivitas.

Kata kunci: *Analisis efektivitas biaya, DM tipe 2, Insulin, Antidiabetik oral.*

Abstract: Diabetes mellitus (DM) type 2 is a group of metabolic diseases with characteristics of hyperglycemia that occurs because of insulin resistance with relative insulin deficiency. Variations in the use of single insulin therapy or a combination of insulin with oral antidiabetics in patients with type 2 DM with inadequate blood glucose control will result in differences in the cost and effectiveness of the therapy. This research is a descriptive study conducted prospectively and follow-up study from May to August 2017. The subjects were 70 patients with type 2 DM who met the inclusion criteria. Data were analyzed to determine the type of therapy and direct medical costs. Therapeutic effectiveness was assessed from achievement of HbA1c target <7% after 3 months follow-up therapy and no adverse drug effects (hypoglycemia). The ACER method is used to analyze the most cost-effective type of insulin therapy. Based on data obtained from the medical record Sanglah Hospital Denpasar, the number of patients with type 2 diabetes mellitus more than 47 people with a percentage of 67.14%, age> 45 years is 63 people with 90.00% percentage. The number of patients with type 2 diabetes mellitus that reaches the target of GDP is 34 people with a percentage of 48.57%, reaching the target of HbA1C is 60 people with 85% percentage. The number of patients with type 2 diabetes mellitus who use aspart insulin aspart therapy with insulin glargine is 42 people with a percentage of 60%. The total direct medical cost that shows the cheapest amount is the use of insulin therapy glargine with metformin is Rp. 274.880,00. Greater therapeutic effectiveness is indicated by a combination of insulin glargine with metformin, 63.63%. Lower cost effectiveness is shown by the type of combination glargine insulin therapy with metformin which is Rp. 4.32 Percentage effectiveness.

Keywords: Cost effectiveness analysis, DM type 2, insulin, oral antidiabetics

PENDAHULUAN

Diabetes mellitus (DM) adalah suatu penyakit gangguan metabolik yang diakibatkan oleh adanya gangguan sekresi insulin, kerja insulin ataupun keduanya (Dipiro *et al.,* 2009). Diabetes mellitus (DM) tipe 2 umumnya terjadi karena kombinasi dari resistensi insulin dan berkurangnya sekresi insulin akibat menurunnya fungsi sel beta pankreas (Tjay dan Rahardja, 2007).

Prevalensi penyakit ini meningkat secara drastis di negara-negara industri dan negara berkembang, termasuk Indonesia. Badan Kesehatan Dunia (*World Health Organization*/WHO) memperkirakan jumlah penderita diabetes mellitus (DM) di Indonesia akan meningkat hingga dua sampai tiga kali lipat pada tahun 2030 dari 8,4 juta mencapai 21,3 juta orang (PERKENI, 2011).

Upaya terapi non farmakologi dan farmakologi telah dilakukan untuk meningkatkan kualitas hidup pasien diabetes mellitus. Terapi farmakologi untuk diabetes mellitus (DM) tipe 2 meliputi antidiabetik oral dan terapi insulin. Insulin diberikan untuk pasien yang memiliki nilai HbA1c ≥7,5% dengan kadar glukosa darah puasa > 250 mg/dL, atau pasien yang gagal dengan terapi antidiabetik oral. Penggunaan insulin dapat dikombinasikan dengan antidiabetik oral apabila kadar glukosa darah tidak terkontrol dengan baik (HbA1c >7,5%) dalam jangka waktu tiga bulan dengan dua antidiabetik oral (Spellman, 2007), sedangkan berdasarkan PERKENI pemberian insulin dapat diberikan pada pasien dengan kadar HbA1c lebih dari 9% (PERKENI, 2011). *American Diabetes Association* (ADA) merekomendasikan penggunaan terapi insulin lebih awal pada pasien DM tipe 2 setelah gagalnya penatalaksanaan terapi melalui manajemen gaya hidup dan monoterapi dengan metformin tunggal (ADA, 2011).

Berdasarkan lama kerjanya,sediaan insulin dibedakan menjadi empat jenis, yaitu insulin kerja cepat, insulin kerja pendek, insulin kerja sedang, dan insulin kerja panjang. Untuk mencapai sasaran glukosa darah basal dipergunakan insulin kerja sedang atau panjang (insulin basal), sedangkan untuk kondisi glukosa darah basal (puasa) telah tercapai tetapi nilaiHbA1c belum mencapai target akan diberikan insulin kerja cepat atau insulin kerja pendek (insulin prandial) (PERKENI, 2011).

Terapi obat pada pasien diabetes mellitus dilakukan seumur hidup sehingga membutuhkan biaya yang sangat besar. Bervariasinya penggunaan terapi obat (terapi insulin tunggal atau kombinasi insulin dengan antidiabetik oral) akan mengakibatkan adanya perbedaan dalam biaya dan luaran terapinya. Jadi, untuk mengetahui efektivitas biaya penggunaan terapi insulin tunggal dan kombinasi insulin dengan antidiabetik oral diperlukan suatu analisis efektivitas biaya (metode yang menilai atau mencari cara yang paling murah dan efektif dalam mencapai target atau suatu tujuan yang sama dengan membandingkan hasil suatu kegiatan dengan biayanya) (Sanchez, 2008).

METODE PENELITIAN

Penelitian tentang analisis efektivitas biaya terapi insulin pada pasien diabetes mellitus tipe 2 rawat jalan di RSUP Sanglah merupakan jenis penelitian deskriptif yang dilakukan secara prospektif dan studi *follow up* (Lwanga dan S. Lemeshow, 1998). Adapun kriteria inklusi dalam penelitian ini sebagai berikut:

a. Pasien berumur diatas 35 tahun.
b. Pasien dengan DM tipe 2dengan kadar GDP ≥126 mg/dL.
c. Pasien yang sedang melakukan kontrol ketika penelitian dilakukan.
d. Pasien yang bersedia menjadi responden.
e. Pasien yang mendapat terapi insulin tunggal atau terapi kombinasi insulin dengan antidiabetik oral.

Demografi Subyek Penelitian

Demografi Subyek Penelitian Berdasarkan Jenis Kelamin. Persentase jumlah subjek berdasarkan jenis kelamin pada pasien DM tipe 2 rawat jalan di RSUP Sanglah Denpasar dapat dilihat pada tabel 1. Jumlah pasien DM tipe 2 lebih banyak diderita oleh laki-laki yaitu sejumlah 47 orang dengan presentase 67,14% dibandingkan dengan perempuan yaitu sejumlah 23 orang dengan presentase 32,86%.

Tabel 1. Karakteristik Pasien DM tipe 2 Berdasarkan Jenis Kelamin

Jenis Kelamin	Jumlah (orang)	Presentase (%)
Laki-Laki	47	67,14
Perempuan	23	32,86
Total	**70**	**100,00**

Demografi Subyek Penelitian Berdasarkan Umur. Persentase jumlah subjek berdasarkan umur pada pasien DM tipe 2 rawat jalan di RSUP Sanglah Denpasardapat dilihat pada tabel 2. Jumlah pasien DM tipe 2 lebih banyak diderita oleh pasien dengan umur >45 tahun yaitu sejumlah 63 orang dengan presentase 90,00% dibandingkan dengan umur ≤45 tahun yaitu sejumlah 7 orang dengan presentase 10,00%.

Tabel 2. Karakteristik Pasien DM tipe 2 Berdasarkan Umur

Kelompok Umur	Jumlah (orang)	Presentase (%)
≤45 tahun	7	10,00
>45 tahun	63	90,00
Total	**70**	**100**

Gambaran Tercapainya Target GDP pada Pasien DM tipe 2 Rawat Jalan RSUP Sanglah Denpasar. Persentase jumlah subjek berdasarkan tercapainya target GDP (90-130 mg/dL) pada pasien DM tipe 2 rawat jalan di RSUP Sanglah Denpasar dapat dilihat pada tabel 3. Jumlah pasien DM tipe 2 yang mencapai target GDP yaitu sejumlah 34 orang dengan presentase 48,57% sedangkan yang tidak mencapai target yaitu sejumlah 36 orang dengan presentase 51,43%.

Tabel 3. Karakeristik Pasien DM tipe 2 Berdasarkan tercapainya GDP

GDP (90-130mg/dL)	Jumlah (orang)	Presentase (%)
Tercapai	34	48,57
Tidak Tercapai	36	51,43
Total	**70**	**100,00**

Gambaran Tercapainya Target HbA1C pada Pasien DM tipe 2 Rawat Jalan RSUP Sanglah Denpasar. Persentase jumlah subjek berdasarkan tercapainya target HbA1C, pada pasien DM tipe 2 rawat jalan di RSUP Sanglah Denpasar dapat dilihat pada tabel 4. Jumlah pasien DM tipe 2 yang mencapai target HbA1C yaitu sejumlah 60 orang dengan presentase 85% sedangkan yang tidak mencapai target yaitu sejumlah 10 orang dengan presentase 15%.

Tabel 4. Karakeristik Pasien DM tipe 2 Berdasarkan tercapainya HbA1c

HbA1C (<9%)	Jumlah (orang)	Presentase (%)
Tercapai	60	85
Tidak Tercapai	10	15
Total	**70**	**100**

Penggunaan Jenis Terapi Insulin pada Pasien DM tipe 2 Rawat Jalan RSUP Sanglah Denpasar. Persentase jumlah subjek berdasarkan penggunaan jenis terapi insulin pada pasien DM tipe 2 rawat jalan di RSUP Sanglah Denpasar dapat dilihat pada tabel 5. Jumlah pasien DM tipe 2 lebih banyak yang menggunakan terapi kombinasi insulin aspart dengan insulin glargine yaitu sejumlah 42 orang dengan presentase 60%, sedangkan yang menggunakan terapi kombinasi insulin glusiline dengan insulin glargine dan metformin lebih sedikit yaitu sejumlah 1 orang dengan presentase 1,43%.

Tabel 5. Penggunaan Jenis Terapi Insulin pada Pasien DM tipe 2

Golongan Obat	Jenis Obat		Jumlah (orang)	Presentase (%)
Insulin Tunggal				
Insulin kerja cepat	Insulin aspart	Novorapid®FlexPen®	6	8,57
Kombinasi				
Insulin kerja cepat + insulin kerja panjang	Insulin aspart + Insulin glargine	Novorapid®FlexPen® + Lantus®FlexPen®	43	61,43
	Insulin glulisine + Insulin glargine	Apidra®FlexPen® + Lantus®FlexPen®	7	10,00
Insulin kerja panjang + Biguanid	Insulin glargine + Metformin	Lantus®FlexPen® + Metformin	11	15,71
Insulin kerja cepat + insulin kerja panjang + Biguanid	Insulin aspart + Insulin glargine + Metformin	Novorapid®FlexPen® + Lantus®FlexPen® + Metformin	2	2,86
	Insulin glulisine + Insulin glargine + Metformin	Apidra®FlexPen® + Lantus®FlexPen® + Metformin	1	1,43

Analisis Efektivitas Biaya Medis Langsung pada Pasien DM tipe 2 Rawat Jalan RSUP Sanglah Denpasar. Persentase jumlah subjek berdasarkan efektivitas biaya medis langsung

pada pasien DM tipe 2 rawat jalan di RSUP Sanglah Denpasar dapat dilihat pada tabel berikut 6. Total biaya medis langsung yang menunjukkan jumlah paling murah dibandingkan dengan yang lainnya adalah penggunaan terapi insulin glargine dengan metformin yaitu sebesar Rp. 274.880,00.

Tabel 6. Biaya Medis Langsung Penggunaan Insulin dan Kombinasi Insulin dengan OHO

Jenis Terapi	B1 (Rp)	R1 (Rp)	B2 (Rp)	B3 (Rp)	B4 (Rp)	B2+B3+ B4 (Rp)	R2 (Rp)	T (Rp)
Insulin aspart	986.571	328.857	92.000	60.000	60.000	212.000	53.000	**381.857**
Insulin aspart + Insulin glargin	1.629.171	543.057	92.000	60.000	60.000	212.000	53.000	**596.057**
Insulin glulisine + Insulin glargin	1.629.171	543.057	92.000	60.000	60.000	212.000	53.000	**596.057**
Insulin glargin + Metformin	665.640	221.880	92.000	60.000	60.000	212.000	53.000	**274.880**
Insulin aspart + Insulin glargin + Metformin	1.652.211	550.737	92.000	60.000	60.000	212.000	53.000	**603.737**
Insulin glulisine + Insulin glargin + Metformin	1.652.211	550.737	92.000	60.000	60.000	212.000	53.000	**603.737**

Keterangan:
B1= biaya obat
B2= biaya laboratorium
B3= biaya pemeriksaan dokter
B4= biaya administrasi
R1= rata-rata biaya obat
R2= rata-rata penjumlahan (B2+B3+B4)
T= total biaya medis langsung tiap bulannya (R1+R2)

Tabel 7. Efektivitas Terapi Penggunaan Insulin dan Kombinasi Insulin dengan antidiabetik oral

Jenis Terapi	Efektivitas Terapi	
	Jumlah (orang)	Presentase (%)
Insulin aspart	2	28,57
Insulin aspart + Insulin glargin	20	47,62
Insulin glulisine + Insulin glargin	4	57,14
Insulin glargin+ Metformin	7	63,63
Insulin aspart + Insulin glargin + Metformin	1	50

Gambaran Efektivitas Terapi Penggunaan Insulin dan Kombinasi Insulin dengan OHO pada Pasien DM tipe 2 Rawat Jalan RSUP Sanglah Denpasar. Persentase jumlah subjek berdasarkan efektivitas terapi penggunaan insulin dan kombinasi insulin dengan OHO pada pasien DM tipe 2 rawat jalan di RSUP Sanglah Denpasar dapat dilihat pada tabel 7. Efektivitas terapi yang lebih besar ditunjukkan oleh jenis terapi kombinasi insulin glargine dengan metformin yaitu sebesar 63,63%, sedangkan efektivitas terapi yang lebih kecil ditunjukkan oleh jenis terapi insulin aspart yaitu sebesar 28,57%.

Efektivitas Biaya Penggunaan Insulin dan Kombinasi Insulin dengan OHO pada Pasien DM tipe 2 Rawat Jalan RSUP Sanglah Denpasar Berdasarkan Metode ACER. Persentase jumlah subjek berdasarkan efektivitas biaya penggunaan insulin dan kombinasi insulin dengan OHO pada pasien DM tipe 2 rawat jalan di RSUP Sanglah Denpasar dengan metode ACER dapat dilihat pada tabel 8. Efektivitas biaya yang lebih rendah ditunjukkan oleh jenis terapi kombinasi insulin glargine dengan metformin yaitu sebesar Rp. 4,32 persentase efektivitas, sedangkan efektivitas biaya yang lebih besar ditunjukkan oleh jenis terapi insulin aspart yaitu sebesar Rp. 13,36 persentase efektivitas.

Tabel 8. Hasil Perhitungan ACER berdasarkan Total Biaya Medis Langsung

Jenis Terapi	Total Biaya Medis Langsung (Rp)	Efektivitas Terapi (%)	ACER (Rp/% efektivitas)
Insulin aspart	381.857	28,57	13,36
Insulin aspart + Insulin glargin	596.057	47,62	12,52
Insulin glulisine + Insulin glargin	596.057	57,14	10,43
Insulin glargin+ Metformin	274.880	63,63	4,32
Insulin aspart + Insulin glargin + Metformin	603.737	50	12,07

PEMBAHASAN

Berdasarkan data yang didapatkan dari rekam medis RSUP Sanglah Denpasar didapatkan sampel pasien diabetes sebanyak 70 pasien yang memenuhi kriteria inklusi. Berdasarkan karakteristik pasien DM tipe 2 dilihat dari jenis kelamin, menunjukkan bahwa DM tipe 2 lebih banyak terjadi pada laki-laki yaitu sebesar 67,14% dengan jumlah 47 orang. Pada laki-laki mempunyai tingkat stres lebih besar dibandingkan dengan perempuan. Stres yang akut cenderung meningkatkan kadar glukosa darah. Stres emosional dapat mempengaruhi gula darah dalam beberapa cara. Manifestasi stres yang paling sering adalah diakibatkan oleh kenaikan dalam hormon stres yang bersikulasi dalam darah. Hormon stres seperti epineprin atau adrenalin dan kortisol, melepaskan glukosa yang disimpan dalam darah, akibatnya adalah kenaikan kadar gula darah yang sering menyebabkan peningkatan insulin (B. Michael, 2012).

Berdasarkan usia, hasil penelitian menunjukkan bahwa pasien DM tipe 2 lebih banyak terjadi pada usia di atas 45 tahun. Semakin bertambahnya usia maka akan terjadi penurunan aktifitas fisik. Berbagai perubahan terkait usia lainnya juga dapat menyebabkan perkembangan diabetes pada orang tua. Ini termasuk penuaan pada sel beta pankreas, dimana pada sel beta pankreas menghasilkan hormon insulin yang berperan penting dalam metabolisme karbohidrat dan juga lemak. Hipersekresi atau produksi berlebih hormon insulin menyebabkan hipoglikemia atau shok insulin. Hiposekresi atau produksi berkurang hormon insulin mengakibatkan hiperglikemia atau Diabetes Mellitus (Nala, 1996). Menurut penelitian semakin tua usia seseorang, insulin yang dikeluarkan juga semakin berkurang dan kemampuan tubuh mempertahankan diri juga semakin berkurang sehingga daya tahan tubuh menurun. Hal ini mempermudah masuknya virus dan dapat merusak pankreas sebagai penghasil insulin (Widharto, 2007). Dalam buku Usada Kencing Manis, menyebutkan bahwa penyakit DM tipe 2 ini juga disebabkan oleh pola dan gaya hidup yang salah, penyakit infeksi, disamping faktor keturunan dan sebab lainnya.

Efektivitas adalah keberhasilan antidiabetik untuk mencapai kadar gula darah menuju target. Target gula darah adalah GDP 90-130 mg/dL (Direktorat Bina Farmasi Komunitas dan Klinik, 2005). Dalam penelitian ini, nilai GDP digunakan sebagai parameter dalam target penatalaksanaan DM. Pada tabel 3 menunjukkan dari 70 orang pasien DM tipe 2, hanya 34 orang atau 48,57% yang mencapai target (GDP 90-130 mg/dL). Hal ini menunjukkan bahwa masih banyak pasien yang memiliki kadar GDP lebih tinggi dari parameter yang telah ditetapkan. Tingginya kadar gula yang dapat memicu terjadinya Diabetes Mellitus disebabkan oleh faktor-faktor gaya hidup dan lingkungan (peningkatan berat badan dan tidak melakukan olahraga secara cukup) (B. Michael, 2012).

Dalam membantu menurunkan kadar gula darah, salah satu cara yang dapat digunakan adalah memberikan terapi farmakologi pada pasien DM tipe 2. Pemberian terapi farmakologi untuk pasien DM tipe 2 dapat diberikan insulin maupun kombinasi antara insulin dengan antidiabetik oral. Pada tabel 5 menunjukkan bahwa penggunaan kombinasi insulin kerja cepat (insulin aspart) dengan insulin kerja panjang (insulin glargine) lebih banyak digunakan. Terapi insulin yang diberikan diupayakan mampu meniru pola sekresi insulin yang fisiologis (PERKENI, 2011).

Pada tabel 5. juga terlihat bahwa penggunaan kombinasi antara insulin kerja panjang (insulin glargine) dengan metformin juga banyak digunakan sebagai terapi, yaitu sejumlah 11 orang. Telah diketahui bahwa metformin mempunyai efek utama menguranggi produksi glukosa di hati (PERKENI, 2011). Kelebihan glukosa yang dihasilkan oleh hati merupakan sumber utama glukosa darah yang tinggi pada Diabetes Mellitustipe 2. Dengan kemampuan dalam menguranggi produksi glukosa di hati, maka metformin digunakan sebagai obat pilihan untuk Diabetes Mellitus tipe 2 (Champe, 2013). Insulin glargine merupakan insulin analog kerja panjang yang diindikasikan untuk memperbaiki kadar glukosa darah puasa pada penderita DM tipe 2. Insulin glargine memberikan fleksibilitas dalam penyesuaian dosis sesuai dengan kebutuhan penderita. Dari beberapa studi "*treat to treat*" dengan insulin glargine ditemukan bahwa hanya pemberian insulin basal ini sering ditemukan kendali glikemik yang baik, dan insulin basal sering diberikan bersamaan dengan metformin (BEU, 2016). Dari hasil penelitian ini menunjukkan bahwa penggunaan kombinasi metformin dengan insulin kerja panjang (insulin glargine), dapat menurunkan kadar GDP sehingga mencapai target. Kombinasi OHO dan insulin basal (insulin kerja panjang) pada umumnya dapat diperoleh kendali glukosa darah yang baik (PERKENI, 2011).

Biaya medis langsung adalah biaya yang paling sering diukur, merupakan *input* yang digunakan secara langsung untuk memberikan terapi (Andayani, 2013). Biaya medis langsung penggunaan insulin dan insulin kombinasi OHO pada pasien DM tipe 2 di rawat jalan RSUP Sanglah ini meliputi biaya obat, biaya pemeriksaan dokter, biaya laboratorium, dan biaya administrasi. Pada tabel 6 menunjukkan bahwa biaya penggunaan kombinasi insulin kerja panjang (insulin glargine) dengan metformin menghabiskan biaya yang lebih rendah dibandingkan dengan yang lainnya yaitu sebesar Rp 274.880,00. Dalam tabel 6 dapat dilihat bahwa biaya laboratorium (B2), biaya pemeriksaan dokter (B3) dan biaya administrasi (B4) tiap pasien sama, hanya saja biaya obat (B1) yang dikeluarkan tiap pasien berbeda. Dengan demikian, besar kecilnya total biaya medis langsung yang dikeluarkan oleh pasien ditentukan oleh besarnya biaya obat. Semakin besar biaya obat maka semakin tinggi pula biaya total medis langsungnya.

Efektivitas terapi pada penelitian ini dilihat daripencapaian target terapi GDP 90-130 mg/dL.Penilaian GDP dilakukan dengan tes GDP (Gula Darah Puasa) di laboratorium. Berdasarkan tabel 7 menunjukkan bahwa penggunan kombinasi insulin kerja panjang (insulin glargine) dengan metformin mempunyai efektivitas terapi yang paling tinggi yaitu 63,63%. Dianjurkan pemberian insulin sebelum tidur sebagai tambahan terapi antidiabetes oral untuk pasien DM tipe 2 yang gagal mendapatkan efek maksimal pada terapi oral. Terapi yang digunakan adalah kombinasi insulin NPH (insulin glargine) sebelum tidur yang dikombinasikan dengan terapi *Biguanide* (metformin) (Katzung, 2002).

Efektivitas biaya merupakan analisis efektivitas biaya dilihat dari sudut pandang rumah sakit, dimana efektivitas yang diukur adalah gula darah pasien yang mencapai target. Perhitungan analisis ini menggunakan perhitungan ACER, dimana ACER diperoleh dari total biaya medis langsung dibagi dengan efektivitas terapi obat tersebut. Semakin rendah nilai ACER maka semakin tinggi nilai *cost effective* suatu kelompok (Alisa, 2015). Pada tabel 8 terlihat bahwa pola pengobatan yang paling *cost effective* adalah terapi kombinasi insulin glargine dengan metformin dengan nilai ACER terkecil sebesar Rp 4,32 persentase efektivitas terapi.

KESIMPULAN

1. Jenis insulin tunggal yang digunakan pada pasien DM tipe 2 rawat jalan di RSUP Sanglah Denpasar adalah insulin aspart. Sedangkan jenis terapi kombinasi insulin dengan antidiabetik oral yang digunakan pasien DM tipe 2 di rawat jalan RSUP Sanglah Denpasar adalah kombinasi insulin glargine dan metformin.
2. Total biaya medis langsung tiap bulan untuk insulin tunggal aspart adalah Rp 381.857,00. Sedangkan total biaya medis langsung tiap bulan untuk kombinasi insulin dengan antidiabetic oral yaitu insulin glargine dan metformin sebesar Rp 274.880,00.
3. Terapi insulin yang paling *cost-effective* berdasarkan ACER yaitu kombinasi insulin glargine dan metformin.

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ANALISIS BIAYA PENGOBATAN PASIEN DIABETES MELLITUS RAWAT JALAN DI RSUD KRATON PEKALONGAN

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ABSTRACT

Diabetes mellitus is a chronic disease that requires long treatment therapy and requires a large cost. This research aims to determine the most cost effective oral antidiabetic treatment of diabetes mellitus type 2 in outpatients in RSUD Kraton Pekalongan. This research type is non experimental research with descriptive method. Data retrieval was conducted in a retrospective study. Processing on the research done by using t-test. The results of the most cost-effectiveness treatment pattern is sulphonylurea and biguanid treatment pattern with an average total cost of Rp. 237.499,44. Value of ACER (Average Cost-Effectiveness Ratio) can be seen from the effectiveness based on blood glucose level reaching target which is equal to 55,56% which is lower if compared with other treatment pattern that is Rp. 427.499,00.

Keywords : *Diabetes mellitus , Oral antidiabetic, ACER, Cost-effectiveness*

Pendahuluan

Diabetes mellitus adalah penyakit gangguan metabolik menahun akibat pankreas tidak memproduksi cukup insulin atau tubuh tidak dapat menggunakan insulin yang diproduksi secara efektif (Depkes RI, 2014). Hiperglikemia yang berhubungan dengan abnormalitas metabolisme karbohidrat, lemak dan protein yang disebabkan oleh penurunan sekresi insulin atau penurunan sensitivitas insulin atau keduanya (Sukandar, dkk, 2008).

Jumlah penderita diabetes mellitus terus mengalami peningkatan setiap tahunnya, terutama untuk diabetes mellitus tipe 2 (Kemenkes RI, 2015). Prevalensi diabetes mellitus tipe 2 sebanyak 90% dari semua kasus diabetes mellitus, seiring bertambahnya usia, hal ini lebih sering terjadi pada wanita daripada pria terjadi pada pasien diabetes mellitus tipe 2 dengan komplikasi (Dipiro dkk, 2008). Sedangkan faktor risiko terjadinya diabetes mellitus tipe 2 tidak disebutkan dipengaruhi oleh jenis kelamin tetapi disebabkan karena gaya hidup pasien diabetes mellitus seperti kelebihan kalori, kurangnya olahraga, obesitas dibandingkan pengaruh genetik (Sukandar dkk, 2008). Menurut Danar tahun 2016 data prevalensi penyakit tidak menular di Kabupaten Pekalongan jumlah pasien diabetes mellitus tipe 2 sebanyak 1421 pasien.

Terapi farmakologis diberikan bersama dengan pengaturan makan dan latihan jasmani seperti gaya hidup sehat. Terapi farmakologis terdiri dari obat oral dan obat bentuk suntikan. Berdasarkan cara kerjanya, obat antihiperglikemia oral dibagi menjadi 5 golongan yaitu: pemacu sekresi insulin atau insulin secretagogue: sulfonilurea dan glinid, peningkat sensitivitas terhadap insulin: metformin dan tiazolidindion (TZD), penghambat absorpsi glukosa: penghambat glikosidase alfa, penghambat dipeptidyl Peptidase-IV (DPP-IV) dan penghambat sodium glucose co-transporter 2 (SGLT-2). Kombinasi yang banyak digunakan adalah kombinasi obat antihiperglikemia oral dan insulin kerja menengah atau insulin kerja panjang (Soelistijo dkk, 2015).

Tujuan penatalaksanaan diabetes mellitus adalah menghilangkan keluhan diabetes mellitus, memperbaiki kualitas

hidup dan mengurangi risiko komplikasi akut dilakukan sebagai tujuan pengobatan jangka pendek, sedangkan tujuan jangka panjang yaitu mencegah dan menghambat progresivitas komplikasi akut dan komplikasi kronik. Tujuan akhir penatalaksanaan terapi yaitu turunnya morbiditas dan mortalitas diabetes mellitus (Soelistijo dkk, 2015).

Studi farmakoekonomi adalah proses identifikasi, pengukuran, membandingkan biaya, risiko dan manfaat dari program pelayanan atau terapi dan menentukan alternatif yang memberikan keluaran kesehatan yang terbaik untuk sumber daya yang digunakan untuk memberikan keluaran optimal rupiah yang dikeluarkan dalam memilih pilihan terapi yang paling cost-effective (Andayani, 2013).

Berdasarkan penelitian yang dilakukan saputri tahun 2016 biaya rata-rata penggunaan golongan obat diabetes mellitus perbulan yang paling murah adalah golongan biguanid. Pola pengobatan antidiabetik oral yang paling *cost-effective* adalah golongan sulfonilurea dan biguanid.

Harga obat-obat antidiabetik sangat bervariasi sehingga harga obat menjadi faktor penting dalam keberhasilan suatu pengobatan diabetes mellitus. Berdasarkan uraian diatas, maka dapat dilihat bahwa terdapat perbedaan biaya terapi diabetes mellitus. Oleh karena itu, peneliti perlu melakukan evaluasi pengobatan antidiabetik oral paling yang paling *cost-effective* pada pasien diabetes mellitus tipe 2 rawat jalan di RSUD Kraton Kabupaten Pekalongan.

METODE PENELITIAN

Desain penelitian yang digunakan dalam penelitian ini adalah non eksperimental dengan metode deskriptif. Pengambilan data dilakukan secara studi retrospektif melalui data rekam medis pasien diabetes mellitus tipe 2. Dilakukan perhitungan biaya terapi diabetes mellitus tipe 2, biaya tes laboratorium dan biaya lainnya seperti biaya administrasi serta biaya periksa dokter dengan tujuan mengetahui efektivitas biaya terapi penyakit diabetes mellitus tipe 2.

Subyek penelitian yang digunakan pada penelitian ini adalah pasien yang memenuhi kriteria inklusi yaitu Pasien rawat jalan yang menderita diabetes mellitus tipe 2 baik laki-laki maupun perempuan umur ≥45 tahun (Dipiro dkk, 2008) di RSUD Kraton Kabupaten Pekalongan, pasien diabetes mellitus tipe 2 dengan yang menggunakan BPJS, Pada terapi pasien diabetes mellitus tipe 2 yang mendapat pola antidiabetik oral yang sama dalam 3 bulan (Freinkel, 2017).

Bahan penelitian ini meliputi data rekam medis pasien diabetes mellitus tipe 2, rincian biaya obat pasien diabetes mellitus tipe 2, rincian biaya tes laboratorium dan rincian jasa dokter di RSUD Kraton Pekalongan.

Alat yang digunakan pada penelitian ini adalah lembar pengumpul data dan penelitian dan data catatan daftar plafon harga obat di RSUD Kraton Pekalongan.

Penelitian ini dilakukan di RSUD Kraton Pekalongan. Waktu penelitian dilakukan pada bulan November 2017 sampai bulan Maret 2018.

Prosedur Kerja

1.Persiapan dan Perizinan

Studi pustaka yang akan digunakan dalam penelitian, permohonan izin untuk melakukan penelitian kepada BAPPEDA LITBANG Kabupaten Pekalongan yang kemudian mendapatkan tembusan surat ke DINKES Kabupaten Pekalongan dan RSUD Kraton Pekalongan, selanjutnya surat diajukan kepada Direktur RSUD Kraton Kabupaten Pekalongan untuk mendapatkan ijin penelitian kemudian disampaikan kepada kepala bagian diklat RSUD Kraton Pekalongan sebagaimana prosedur resmi untuk melakukan penelitian di RSUD Kraton Pekalongan. Setelah itu kebagian Kepala Instalasi Rekam Medis, Kepala Instalasi Farmasi dan ke bagian Bendahara Penerimaan di RSUD Kraton Pekalongan.

2. Pengumpulan Data

Pengambilan data dilakukan di RSUD Kraton Pekalongan dengan menggunakan teknik observasi dengan cara mencatat data-data rincian biaya yang

dikeluarkan oleh pasien rawat jalan. Pengumpulan data dilakukan dengan mengambil data dari bagian instalasi rekam medis, instalasi farmasi dan bagian bendahara penerimaan di RSUD Kraton Pekalongan menggunakan lembar pengumpul data. Data yang dikumpulkan dalam penelitian ini berupa informasi data pasien meliputi data rekam medis pasien, biaya terapi diabetes mellitus tipe 2, biaya tes laboratorium dan biaya lainnya seperti biaya administrasi serta biaya jasa dokter.

Data yang dicatat pada lembar pengumpul data meliputi nomor rekam medis, identitas pasien meliputi nama, usia dan jenis kelamin, diagnosis meliputi utama dan data laboratorium, obat yang diberikan meliputi macam, waktu pemberian, cara pemberian dan dosis obat, data biaya obat, data biaya tes laboratorium dan data biaya administrasi.

3. Analisis Data

Data diolah dengan menggunakan SPSS (Statistical Package for the Social Sciences) versi 21.

Perhitungan Efektivias Terapi

Persentase gula darah mencapai target dihitung dari jumlah data gula darah terkontrol terhadap total data gula darah. Persentase gula darah terkontrol ini dikelompokkan berdasarkan riwayat menderita diabetes mellitus dan pola terapi, kemudian dianalisis untuk mendapatkan rata-rata dengan rumus :

$$\text{Efektivitas}(\%) = \frac{\text{Total ukur gula darah mencapai target}}{\text{Total pasien}} \times 100$$

Perhitungan Efektivitas Biaya Terapi

Perhitungan efektivitas biaya terapi dilakukan sesuai dengan sudut pandang rumah sakit. Efektivitas biaya dapat dilihat dari nilai average cost-effectiveness ratio (ACER) dan incremental cost-effectiveness. Terapi yang cost-effective adalah terapi yang mempunyai biaya netto yang paling rendah per unit efektivitas (Andayani, 2013).

$$\text{ACER} = \frac{\text{Biaya rata} - \text{rata jenis terapi obat}}{\text{Efektivitas (\%)}}$$

Hasil Penelitian

Hasil penelitian yang dilakukan peneliti diperoleh data sebagai berikut:

1. Data Distribusi Pasien Di RSUD Kraton Pekalongan
   a. Data Distribusi Pasien Berdasarkan Jenis Kelamin

Data distribusi pasien berdasarkan jenis kelamin dapat dilihat pada tabel 1.

Tabel 1. Distribusi pasien berdasarkan jenis kelamin

No.	Jenis Kelamin	Jumlah	Persentase
1	Laki-laki	23	52,3
2	Perempuan	21	47,7
Total		**44**	**100**

   b. Data Distribusi Pasien Berdasarkan Umur

Data rekam medis diperoleh sampel yang memenuhi kriteria inklusi sebesar 44 pasien. Subyek penelitian dikelompokkan dari umur 30-45 tahun, 46-55 tahun dan ≥56 tahun. Data distribusi pasien berdasarkan umur dapat dilihat pada tabel 2.

Tabel 2. Distribusi pasien berdasarkan umur

No.	Umur	Jumlah	Persentase
1	30-45 tahun	1	2,3
2	46-55 tahun	12	27,3
3	≥ 56 tahun	31	70,5
Total		**44**	**100**

   c. Data Distribusi Pasien Berdasarkan Diagnosis

Data rekam medis di ruang *filling* rekam medis RSUD Kraton Pekalongan, data pasien yang terdiagnosa diabetes mellitus tipe 2 sebanyak 44 pasien sehingga dapat disimpulkan bahwa dalam penelitian ini data

yang diambil peneliti 100% pasien yang terdiagnosa diabetes mellitus tipe 2.

d. Data Pengukuran Kadar Gula Darah Berdasarkan Pola Terapi Pengobatan.

Data penelitian hasil pengukuran kadar gula darah pasien berdasarkan pola terapi pengobatan dapat dilihat pada tabel 3. Berdasarkan data rekam medis di ruang filling rekam medis RSUD Kraton Pekalongan dari 44 pasien yang memenuhi kriteria inklusi penelitian dan dari seluruh pasien tersebut hanya 17 pasien (38,6%) yang memenuhi target penurunan kadar gula darah.

Tabel 3. Distribusi pasien berdasarkan kategori kadar gula darah

No	Kadar gula dalam darah	Jumlah	Persentase
1	Tidak sesuai target	27	61,4
2	Sesuai target	17	38,6
	Total	**44**	**100**

e. Data Distribusi Pasien Berdasarkan Lama Rawat Jalan

Pada penelitian ini lama rawat jalan, berdasarkan data rekam medis yaitu pasien yang telah melakukan 3 kali pengobatan dan mendapatkan terapi antidiabetik oral yang sama.

f. Gambaran Terapi Pengobatan Pasien Diabetes Mellitus tipe 2

Hasil penelitian yang dilakukan oleh peneliti di RSUD Kraton Pekalongan terapi antidiabetik oral yang digunakan adalah golongan sulfonilurea, biguanid, penghambat α-glikosidase dan tiazolidinedion. Data hasil penelitian dapat disajikan pada tabel 4.

Tabel 4. Gambaran terapi pengobatan diabetes mellitus tipe 2

No	Terapi diabetes mellitus tipe 2	Nama obat	Jumlah pasien	Persentase
1	Sulfonilurea	Glimepiride 1mg	21	47,73%
		Glurenorm 15 mg	1	2,27%
		Gliquidon 30mg	6	13.64%
		Glucodex 80 mg	3	6,82%
	Total		**31**	**70,45%**
2	Biguanid	Metformin 500 mg	30	68,18%
	Total		**30**	**68,18%**
3	α-GLIKOSIDASE	Acarbose 50 mg	29	65,91%
	Total		**29**	**65,91%**
4	Tiazolidinedion	Pioglitazone 15 mg	2	4,55%
		Deculin 15 mg	3	6,82%
		Pionix 30 mg	2	4,55%
	Total		**7**	**15,91%**

g. Biaya Antidiabetik Oral, Biaya Penunjang, Biaya Tambahan

Biaya antidiabetik oral adalah biaya terapi diabetes mellitus tipe 2 yang digunakan oleh pasien berdasarkan harga satuan obat antidiabetik dikalikan dengan jumlah pemakaian obat per hari yang diberikan selama 1 bulan, dalam penelitian ini diasumsikan pasien menerima resep untuk 1 bulan penuh. Gambaran biaya rata-rata diabetes mellitus tipe 2 dapat dilihat pada tabel 5.

Tabel 5. Gambaran Gambaran biaya rata-rata diabetes mellitus tipe 2

No	Pola Pengobatan	N	Biaya rata-rata DM (Rp) ± SD	
1	S	4	19042,5 ±	14566,54472
2	S+B	9	34440,00 ±	34829,04
3	S+α-GLIKOSIDASE	6	79450 ±	10456,20581
4	B+ α-GLIKOSIDASE	4	77580 ±	0
5	S+TZD	1	125250 ±	0
6	B+TZD	2	65880 ±	0
7	α-GLIKOSIDASE+TZD	1	204090 ±	0
8	S+B+ α-GLIKOSIDASE	14	83487,857 ± 14	328,7313276
9	S+ α-GLIKOSIDASE+TZD	1	192643 ±	0
10	B+ α-GLIKOSIDASE+TZD	1	212550 ±	0
11	S+B+TZD	1	107880 ±	0

2. Efektivitas Biaya

Analisis efektivitas biaya dari sudut pandang rumah sakit RSUD Kraton Pekalongan, dimana efektivitas atau keluaran yang diukur adalah pasien yang kadar glukosa darahnya mencapai target yang diharapkan. Data gambaran efektivitas biaya terapi pengobatan diabetes mellitus tipe 2 disajikan pada tabel 6.

Tabel 6. Gambaran efektivitas biaya terapi pengobatan diabetes mellitus tipe 2

Pola pengobatan	Rata-rata biaya botal	Keefektifan (%)	ACER (Rp)
	228371,25	50,00%	456742,50
+B	237499,44	55,56%	427499,00
+α-GLIKOSIDASE	294399,6667	33,33%	883199,00
+ α-GLIKOSIDASE	336730,75	50,00%	673461,50
+TZD	299790	0,00%	0,00
+TZD	309674	50,00%	619348,00
-GLIKOSIDASE+TZD	439650	0,00%	0,00
+B+ α-GLIKOSIDASE	299556,2857	35,71%	838757,60
+ α-LIKOSIDASE+TZD	373483	0,00%	0,00
+ α-LIKOSIDASE+TZD	381000	0,00%	0,00
+B+TZD	320430	0,00%	0,00

Pembahasan

Hasil penelitian yang dilakukan peneliti didapatkan sejumlah 44 pasien yang telah memenuhi kriteria inklusi penelitian sebanyak 23 pasien (52,3%) laki-laki dan 21 pasien (47,7%) perempuan, hal ini dengan persentase sebesar 70,5%, sedangkan pasien dengan umur 46-55 tahun dengan persentase sebesar 27,3% dan sebesar 2,3% untuk pasien dengan umur 30-45 tahun. Berdasarkan hasil penelitian diperoleh kesesuaian bahwa diabetes mellitus tipe 2 banyak terjadi pada pasien dengan umur lebih dari 45 tahun. Jumlah pasien diabetes mellitus tipe 2 akan meningkat sejalan dengan pertambahan umur (Lathifah, 2017). Target penurunan gula darah tergantung pada keadaan individu pasien, tingginya kadar gula darah pasien dan berdasarkan usia. Target penurunan kadar gula darah yang diharapkan adalah untuk glukosa darah puasa (GDP) antara 90-130 mg/dl, gula darah 2 jam setelah makan atau gula darah post prandial (GD2PP) antara 110-180 mg/dl atau gula darah sewaktu (GDS) <180 mg/dl (Soelistijo dkk, 2015). Distribusi lama rawat jalan pasien Diabetes mellitus tipe 2 sesuai dengan PERKENI berdasarkan algoritme pengelolaan diabetes mellitus tipe 2 yaitu menggunakan obat yang sama dalam 3 bulan (Soelistijo dkk, 2015). Hal tersebut juga diperkuat dengan penelitian yang dilakukan

menujukkan bahwa prevalensi terjadinya diabetes mellitus tipe 2 lebih besar terjadi pada laki-laki. Faktor risiko terjadinya diabetes mellitus tipe 2 tidak disebutkan dipengaruhi oleh jenis kelamin tetapi disebabkan karena gaya hidup pasien diabetes mellitus seperti kelebihan kalori, kurangnya olahraga, obesitas dibandingkan pengaruh genetik (Sukandar dkk, 2008). Subyek penelitian dikelompokkan dari umur 30-45 tahun, 46-55 tahun dan ≥56 tahun. Hal ini dimaksudkan agar terlihat jelas angka kejadian diabetes mellitus tipe 2 pada masing-masing umur. Menurut Dipiro, 2008 faktor risiko terjadinya diabetes mellitus tipe 2 pada umur ≥45 tahun berisiko lebih tinggi terkena diabetes mellitus tipe 2 dibandingkan umur <45 tahun. Data hasil penelitian pada tabel 2 menunjukkan bahwa pasien diabetes mellitus tipe 2 lebih banyak terjadi pada pasien dengan umur ≥ 56 tahun

Baroroh dkk tahun 2016 pengobatan diabetes mellitus tipe 2 yaitu minimal 3 kali pengobatan atau kunjungan terapi atau merupakan pasien lama yang mendapatkan obat antidiabetik oral yang sama. Berdasarkan data rekam medis di RSUD Kraton Kabupaten Pekalongan terapi pengobatan diabetes mellitus tipe 2 yang paling banyak digunakan yaitu golongan sulfonilurea sebanyak 31 pasien (70,45%). Hal tersebut memiliki kesesuaian dengan penelitian yang dilakukan Saputri pada tahun 2016 bahwa terapi antidiabetik oral yang paling banyak digunakan adalah golongan sulfonilurea karena sulfonilurea merupakan pilihan utama untuk pasien dengan berat badan normal dan kurang. Berdasarkan hasil penelitian yang sudah dilakukan di RSUD Kraton Pekalongan biaya pengobatan diabetes mellitus tipe 2, biaya yang menggunakan obat monoterapi lebih murah dibandingkan dengan penggunaan obat kombinasi Biaya penggunaan obat diabetes mellitus tipe 2 yang paling murah adalah golongan sulfonilurea yaitu sebesar Rp. 19.042,5 ± 14.566,55 dan yang paling mahal adalah obat kombinasi golongan

sulfonilurea+biguanid+α-glikosidase yaitu sebesar Rp. 83.487,86 ± 328.73. Biaya penunjang adalah biaya yang harus dikeluarkan pasien meliputi biaya administrasi dan biaya dokter di RSUD Kraton Pekalongan. Diasumsikan bahwa pasien periksa satu kali untuk satu bulan penuh yaitu 30 hari. Biaya penunjang yang harus dikeluarkan pasien diabetes mellitus tipe 2 yaitu sebesar Rp. 68.000,00 setiap kali kontrol rawat jalan. Biaya tambahan adalah biaya yang harus dikeluarkan pasien yaitu biaya pemeriksaan laboratorium. Tes pemeriksaan berdasarkan tarif laboratorium di RSUD Kraton Pekalongan. Pemeriksaan laboratorium untuk pasien diabetes mellitus tipe 2 adalah pemeriksaan gula darah meliputi glukosa darah puasa (GDP), glukosa darah 2 jam post prandial (GD2JPP). Diasumsikan bahwa pasien melakukan pemeriksaan laboratorium satu kali untuk satu bulan penuh yaitu 30 hari. Biaya rata-rata pemeriksaan laboratorium yang harus dikeluarkan pasien yaitu sebesar Rp. 73.000,00 setiap bulannya. Analisis efektivitas biaya dihitung dalam bentuk ACER (*Average Cost-Efeectiveness Ratio*). Data hasil penelitian yang dilakukan oleh peneliti diperoleh nilai ACER pola pengobatan golongan sulfonilurea dan biguanid lebih *cost effective* yaitu sebesar Rp. 427.499,00 dibanding dengan pola pengobatan yang lain. Pola pengobatan golongan sulfonilurea dan biguanid mempunyai nilai ACER yang paling rendah dibandingkan dengan pola pengobatan yang lain. Menurut Andayani tahun 2013 Semakin rendah nilai ACER maka semakin tinggi nilai *cost- effective* suatu pola pengobatan.

Simpulan

Berdasarkan penelitian yang dilakukan dapat ditarik kesimpulan sebagai berikut: Pola pengobatan yang paling *cost-effectiveness* pada pasien diabetes mellitus tipe 2 adalah pola pengobatan sulfonilurea+biguanid dengan rata-rata biaya total Rp. 237.499,44. Nilai ACER (*Average Cost-Efeectiveness Ratio*) yang paling rendah dibandingkan dengan pola pengobatan yang lain yaitu Rp. 427.499,00. Perlu dilakukan analisis efektivitas biaya diabetes mellitus tipe 2 dengan menggunakan sampel yang lebih banyak dan perlu dilakukan analisis efektivitas biaya dengan memperhatikan pola hidup pasien dan kepatuhan pasien dalam mengkonsumsi obat antidiabetik.

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ORIGINAL RESEARCH

Cost-Effectiveness Analysis of Incretin Therapy for Type 2 Diabetes in Spain: 1.8 mg Liraglutide Versus Sitagliptin

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ABSTRACT

Objectives: Metformin is the first-line therapy for most patients with type 2 diabetes, but the majority require treatment intensification at some stage due to the progressive nature of the disease. The 1860-LIRA-DPP-4 trial showed that liraglutide exhibited greater improvements compared with sitagliptin in glycated hemoglobin and body mass index in patients with type 2 diabetes inadequately controlled on metformin monotherapy. As a follow-up to a previously published cost-effectiveness analysis of 1.2 mg liraglutide versus sitagliptin in Spain, the aim of this analysis was to compare long-term projections of the clinical and cost implications associated with 1.8 mg liraglutide and sitagliptin.

Methods: For the modeling analysis, 52-week treatment effect data (as opposed to 26-week data in the previous analysis) were taken from the 1860-LIRA-DPP-4 trial, for adults with type 2 diabetes receiving 1.8 mg liraglutide or 100 mg sitagliptin daily in addition to metformin. Long-term (patient lifetime) projections of clinical outcomes and direct costs (2012 EUR) were made using a published and validated model of type 2 diabetes, with modeling assumptions as per the 1.2 mg liraglutide analysis.

Results: Liraglutide was associated with increased life expectancy (14.24 versus 13.87 years) and quality-adjusted life expectancy [9.24 versus 8.84 quality-adjusted life years (QALYs)] over sitagliptin. Improved clinical outcomes were attributable to the improvement in glycemic control, leading to a reduced incidence of diabetes-related complications, including renal disease, cardiovascular disease, ophthalmic and diabetic foot complications. Liraglutide was associated with increased direct costs (EUR 56,628 versus EUR 52,450), driven by increased pharmacy costs. Based on these estimates, liraglutide was associated with an incremental cost-effectiveness ratio of EUR 10,436 per QALY gained versus sitagliptin.

Conclusions: A previous analysis has suggested that 1.2 mg liraglutide is cost-effective from a healthcare payer perspective in Spain, and the present analysis suggests that the 1.8 mg dose is also likely to be cost-effective.

Keywords: Cost; Cost-effectiveness; Incretin; Liraglutide; Sitagliptin; Spain; Type 2 diabetes

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INTRODUCTION

Hyperglycemia in type 2 diabetes results from insulin resistance in the peripheral tissues, insulin deficiency due to insufficient pancreatic output, and excessive hepatic glucose output and is associated with serious microvascular and macrovascular complications [1]. Early initiation of treatment can delay disease progression, and achieving evidence-based clinical goals by implementing effective management strategies substantially reduces the risk of morbidity and mortality and ultimately improves patient outcomes [2–4].

Metformin remains the first-line therapy for most patients with type 2 diabetes mellitus. However, due to the progressive nature of the disease, with beta cell function declining over time, the majority of patients require additional therapy to maintain glycemic control. Long-standing second-line interventions include sulfonylureas and thiazolidinediones, and whilst these therapies are effective in achieving glycemic control, they are associated with weight gain, increased risk of hypoglycemic events, and/or cardiovascular concerns [5].

In an attempt to improve treatment of type 2 diabetes, a number of new therapies targeting the incretin axis have been developed [6]. These therapies exert effects in a number of different target tissues to address the complex pathophysiology of the disease. Incretin-based therapy has been shown to stimulate glucose-dependent insulin secretion, reduce glucagon secretion, improve beta cell function, slow gastric emptying, increase satiety, reduce appetite, and general benefits beyond the pancreas. Two classes of incretin therapy have been developed: degradation-resistant glucagon-like peptide-1 (GLP-1) receptor agonists (such as liraglutide and exenatide) which mimic the actions of endogenous GLP-1, and dipeptidyl peptidase-4 (DPP-4) inhibitors (such as sitagliptin and saxagliptin) which inhibit the inactivation of incretin hormones by the enzyme DPP-4. Both GLP-1 receptor agonists and DPP-4 inhibitors are associated with reductions in glycated hemoglobin (HbA1c), but reductions may be more substantial with GLP-1 receptor agonists (0.5–1.6% reduction versus 0.5–1% reduction) [7]. Furthermore, GLP-1 receptor agonists are associated with weight loss [8–13] whereas DPP-4 inhibitors have been associated only with the prevention of weight gain [14–17].

Whilst the interventions that target the incretin axis provide a more rounded approach to treatment of type 2 diabetes than traditional second-line interventions, they also come at an increased cost in the short term, although this can be partially offset by avoidance of treatment of diabetes-related complications over a patient's lifetime as a result of better control. In a publically funded healthcare system, such as Spain, the aim is to maximize health outcomes across the population with the finite resources available. Healthcare payers must make decisions on how best to allocate these scarce resources, and economic evaluation of new and existing healthcare interventions is playing an increasingly important role in informing these decisions [18, 19].

A previous study investigating the cost-effectiveness analysis of liraglutide 1.2 mg versus sitagliptin in the Spanish setting demonstrated that liraglutide was associated with improved life expectancy and quality-adjusted life expectancy but was associated with increased costs [20]. The analysis concluded that liraglutide 1.2 mg was cost-effective compared to sitagliptin over patient lifetimes. However, liraglutide is available in two doses, either 1.2 or 1.8 mg per day. The liraglutide trial program has shown that the increased dose is associated with improved clinical outcomes over the lower dose, but this increased efficacy comes at an increased pharmacy cost.

As a follow-up analysis to the previously published cost-effectiveness analysis of liraglutide 1.2 mg versus sitagliptin, the present analysis aimed to assess the cost-effectiveness of liraglutide 1.8 mg versus sitagliptin in patients failing to achieve adequate glycemic control on metformin monotherapy in the Spanish setting. A secondary analysis was also conducted, in which the cost-effectiveness of delaying GLP-1 receptor agonist therapy, with a year of DPP-4 inhibitor therapy first, was investigated.

METHODS

Modeling Analysis

The present analysis is a further extension of the cost-effectiveness analysis of liraglutide 1.2 mg versus sitagliptin in Spain, with two major differences. The first is the evaluation of the 1.8 mg dose of liraglutide (rather than the 1.2 mg dose), and the second is the use of trial data from the 52-week endpoint (rather than the 26-week endpoint). The methods used in this analysis are consistent with the previously published cost-effectiveness analysis of liraglutide 1.2 mg versus sitagliptin, and therefore are only outlined briefly here [20]. The analysis was performed using the CORE Diabetes Model (IMS Health, Basel, Switzerland), a non-product specific diabetes policy analysis tool. The model functionality has been previously described, and the long-term outcomes projected by the model have been validated against real-life data at first publication in 2004 and following a series of updates in 2013 [21–23].

The model was used to project life expectancy, quality-adjusted life expectancy, cumulative incidence of diabetes-related complications, time to onset of diabetes-related complications and direct medical costs for patients receiving liraglutide 1.8 mg daily or sitagliptin 100 mg daily in the Spanish setting.

In line with published health economic guidance for Spain, future costs and clinical benefits were discounted symmetrically by 3% per annum [24]. The time horizon was set to patient lifetimes in the base case to capture all relevant long-term complications, associated costs, and to assess their impact on life expectancy and quality-adjusted life expectancy.

Simulated Cohort

The baseline cohort characteristics were taken from the 1860-LIRA-DPP-4 (NCT00700817) trial [25, 26]. This study enrolled patients with type 2 diabetes mellitus who had inadequate glycemic control (HbA1c 7.5–10.0%) on metformin (≥1500 mg daily for ≥3 months) in Europe

(including 9 centers in Spain) and North America. Patients were randomly allocated to 1.2 mg subcutaneous liraglutide once daily ($n = 225$), 1.8 mg subcutaneous liraglutide once daily ($n = 221$) or 100 mg oral sitagliptin once daily ($n = 219$). Mean age of the cohort was 55.3 years [standard deviation (SD) 9.2 years], with mean duration of diabetes of 6.0 years (SD 4.5 years), mean HbA1c of 8.4% (SD 0.80%), and mean body mass index (BMI) of 32.8 kg/m^2 (SD 5.2 kg/m^2).

Treatment Effects and Risk Factor Progression

In the previously published cost-effectiveness analysis of liraglutide 1.2 mg daily, treatment effect data were taken from the 26-week primary endpoint [20, 25]. In the present analysis, the treatment effects applied in the first year of the modeling analysis (Table 1) were taken from the 52-week time point as this longer follow-up data may represent a more robust source for long-term modeling, although it was not the primary endpoint of the trial (a sensitivity analysis using the primary endpoint data was conducted) [26]. Assumptions regarding progression of risk factors in the following years of the simulation were aligned with the cost-effectiveness analysis of liraglutide 1.2 mg versus sitagliptin [20]. HbA1c was assumed to remain unchanged for the duration of the analysis, as this allows the modeling analysis to capture the legacy effect, where benefits of reductions in HbA1c early in a patient's life persist even after the HbA1c reduction has been abolished. Systolic blood pressure increased based on the UKPDS progression equation, whilst serum lipids followed the Framingham progression equations [21]. As in the previous analysis, patients were assumed to receive incretin therapy for 5 years, before intensifying treatment to basal insulin (with the previously received incretin therapy withdrawn). On treatment intensification, BMI was assumed to return to baseline and hypoglycemia event rates were assumed to be the same in both arms, but no other treatment effects were applied.

Table 1 Treatment effects applied in the first year of the base case analysis

Physiological parameter	Liraglutide 1.8 mg		Sitagliptin 100 mg		Difference
	Mean	SD	Mean	SD	
Change in HbA1c (%)	−1.51	1.02	−0.88	1.04	−0.63*
Change in SBP (mmHg)	−2.55	13.83	−1.03	13.76	−1.52
Change in total cholesterol (mg/dL)	−3.48	28.74	1.16	34.34	−4.64
Change in HDL cholesterol (mg/dL)	0.77	5.75	0.39	5.72	0.39
Change in LDL cholesterol (mg/dL)	3.48	28.74	6.57	28.61	−3.09
Change in triglycerides (mg/dL)	−28.34	131.67	−20.37	131.07	−7.97
Change in body mass index (kg/m^2)	−1.25	–	−0.33	–	−0.89*
Major hypoglycemic events (per 100 patient years)	0.00	–	0.00	–	0.00
Minor hypoglycemic events (per 100 patient years)	15.40	–	13.70	–	1.70

HbA1c glycated hemoglobin, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *SBP* systolic blood pressure, *SD* standard deviation

* $p < 0.001$ [26]

Costs and Utilities

Costs were accounted from the perspective of a healthcare payer in Spain in 2012 EUR. All costs were as per the previous cost-effectiveness evaluation of liraglutide 1.2 mg versus sitagliptin in Spain [20]. Utilities were in line with the previous cost-effectiveness analysis in Spain, and a cost-effectiveness analysis of liraglutide versus sitagliptin carried out in the UK setting [20, 27]. Full details of the costs and utilities are provided in the online supplementary information.

Sensitivity Analyses

A number of sensitivity analyses were conducted to evaluate the robustness of the modeled outcomes to changes in input parameters, and to identify key drivers of results. These were consistent with the previously published analysis of liraglutide 1.2 mg versus sitagliptin [20].

Scenarios with time horizons of 5, 10, 20 and 30 years, compared to 50 years in the base case, were run to evaluate the influence of the time horizon of the analysis on the projected outcomes. The effect of application of discount rates of 0% and 5% per annum on future cost and clinical outcomes was also investigated. The costs of diabetes-related complications were increased/decreased by 10% from those used in the base case analysis to examine the influence of over- or underestimating these costs. The importance of changes in physiological parameters were investigated in five sensitivity analyses, in which benefits in HbA1c, systolic blood pressure, blood lipids, BMI and hypoglycemia were individually abolished. Two scenarios with alternative assumptions around long-term progression of HbA1c were investigated. In the first, the HbA1c difference between the treatment arms was abolished when patients switched to insulin therapy. In the second, the United Kingdom Prospective Diabetes Study progression for HbA1c (as described by Palmer et al. [21]) was followed whilst patients received incretin therapy, and then HbA1c remained constant when patients switched to insulin. The effect of the timing of treatment switching was examined by varying the treatment switch to 7 and 3 years in both arms. A scenario was also investigated in which the 26-week primary endpoint data were used to inform the treatment effects used in the first year of the analysis.

Secondary Analysis

As a further extension to the 1860-LIRA-DPP-4 trial, patients in the sitagliptin arm completing 52 weeks of treatment were randomly allocated to receive either liraglutide 1.2 mg or liraglutide 1.8 mg for a further 26 weeks [28]. Switching patients from sitagliptin to liraglutide 1.8 mg was associated with a further reduction in HbA1c and BMI, although these improvements were not as extensive as when liraglutide was initiated in the first year of the trial (Table 2). However, hypoglycemic event rates were lower than when liraglutide was initiated earlier. This may have been as a result of patients with a high susceptibility to hypoglycemia dropping out of the study (only 62% of the patients originally randomly allocated to sitagliptin entered the extension study at 52 weeks). A secondary cost-effectiveness analysis was conducted based on this extension to the 1860-LIRA-DPP-4 trial. In this comparison, 1 year of sitagliptin therapy followed by 4 years of liraglutide therapy was compared with 5 years of sitagliptin therapy (as in the base case analysis), with patients in both arms switched to insulin at the end of year five. All other assumptions were as per the base case analysis, and equivalent sensitivity analyses were performed.

This article does not contain any new studies with human or animal subjects performed by any of the authors.

Table 2 Treatment effects applied in the secondary analysis on switching from sitagliptin to liraglutide 1.8 mg after 1 year of therapy

Physiological parameter	Mean	Standard deviation
Change in HbA1c (%)	−0.50	1.16
Change in SBP (mmHg)	0.40	18.08
Change in total cholesterol (mg/dL)	−7.72	34.33
Change in HDL cholesterol (mg/dL)	0.00	34.33
Change in LDL cholesterol (mg/dL)	−11.58	11.44
Change in triglycerides (mg/dL)	−26.55	4.57
Change in body mass index (kg/m^2)	−0.87	–
Major hypoglycemic events (per 100 patient years)	0.00	–
Minor hypoglycemic events (per 100 patient years)	3.10	–

HbA1c glycated hemoglobin, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *SBP* systolic blood pressure

RESULTS

Base Case Analysis

Treatment with liraglutide 1.8 mg was associated with a mean increase in discounted life expectancy of 0.37 years over treatment with sitagliptin (Table 3). Liraglutide was also associated with mean quality-adjusted life expectancy of 9.24 quality-adjusted life years (QALYs), compared to 8.84 QALYs with sitagliptin, a difference of 0.40 QALYs. The clinical benefits in the liraglutide arm were primarily driven by improved glycemic control with liraglutide over sitagliptin, resulting in a reduction in the projected incidence of all diabetes-related complications over patient lifetimes. Of particular note were the reductions in cumulative incidence of diabetic retinopathy, falling from 17.3% to 13.9% (relative risk reduction of 20.1%), and neuropathy, falling from 48.5% to 40.4% (relative risk reduction of 16.7%). The mean time to onset of diabetes-related complications was increased with liraglutide (Fig. 1). The mean time free from any complication was increased from 6.2 years with sitagliptin to 7.4 years with liraglutide, an increase of approximately 20%.

Liraglutide was associated with increased direct costs of EUR 4177 per patient versus sitagliptin (EUR 56,628 versus EUR 52,450) (Table 3; Fig. 2). The increased acquisition cost of liraglutide over sitagliptin (accrued during the first 5 years of the analysis) drove this difference. However, the reduced costs of treating diabetes-related complications partially offset this increased cost. The most notable savings were made as a result of avoided diabetic foot complications, where mean savings of EUR 2173 per patient were made (EUR 17,901 versus EUR 20,074).

Table 3 Cost-effectiveness outcomes of the base case analysis

	Liraglutide 1.8 mg [mean (SD)]	Sitagliptin [mean (SD)]	Difference
Life expectancy (years)	14.241 (0.183)	13.873 (0.185)	+0.368
Quality-adjusted life expectancy (QALYs)	9.239 (0.121)	8.838 (0.121)	+0.400
Direct costs (EUR)	56,628 (1323)	52,450 (1394)	+4177
ICER (EUR per QALY gained)	10,436		

N.B: ICERs calculated based on the incremental costs and quality-adjusted life expectancy values shown in the table differ from the ICER shown in the bottom row of the table due to rounding
EUR 2012 Euros, *ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life year, *SD* standard deviation

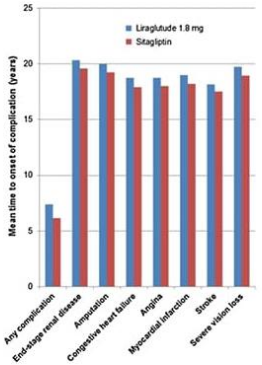

Fig. 1 Mean time to onset of diabetes-related complications with liraglutide and sitagliptin

Based on these estimates, liraglutide 1.8 mg was associated with an incremental cost-effectiveness ratio (ICER) of EUR 10,436 per QALY gained versus sitagliptin. Analysis of the incremental outcomes of the 1000 cohorts of 1000 patients run through the model found that in 97.7% of iterations, liraglutide was

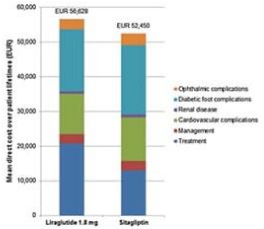

Fig. 2 Mean direct costs with liraglutide and sitagliptin over patient lifetimes. *EUR* 2012 Euros

associated with increased quality-adjusted life expectancy and increased direct costs. In 95% of iterations, liraglutide was associated with an ICER of less than EUR 30,000 per QALY gained versus sitagliptin.

Sensitivity Analyses

Sensitivity analyses found that the cost-effectiveness outcomes were most sensitive to changes in the time horizon of the modeling analysis, with liraglutide less cost-effective over shorter time horizons (Table 4). As the time horizon was reduced, the ICER increased, with a 5-year time horizon producing an ICER of EUR

Table 4 Summary of results of sensitivity analyses

Analysis	Quality-adjusted life expectancy (QALYs)			Direct costs (EUR)			ICER (EUR per QALY gained)
	Liraglutide	Sitagliptin	Difference	Liraglutide	Sitagliptin	Difference	
Base case	9.239	8.838	0.400	56,628	52,450	4177	10,436
30-year time horizon	9.045	8.698	0.347	53,418	49,347	4071	11,740
20-year time horizon	8.163	7.915	0.248	43,975	39,387	4589	18,485
10-year time horizon	5.406	5.294	0.112	26,378	20,083	6295	56,263
5-year time horizon	3.096	3.036	0.060	16,564	9524	7040	116,534
0% discount rate	12.926	12.243	0.683	87,350	83,764	3585	5251
5% discount rate	7.647	7.352	0.295	44,666	40,250	4416	14,955
Costs of complications +10%	9.239	8.838	0.400	60,037	56,221	3816	9534
Costs of complications −10%	9.239	8.838	0.400	53,390	48,858	4532	11,323
No HbA1c difference	8.939	8.838	0.101	59,869	52,450	7418	73,626
No SBP difference	9.228	8.838	0.390	56,843	52,450	4393	11,264
No lipid difference	9.193	8.838	0.354	56,742	52,450	4292	12,119
No BMI difference	9.195	8.838	0.356	56,596	52,450	4146	11,633
No hypoglycemia difference	9.236	8.838	0.398	56,606	52,450	4156	10,450
HbA1c difference abolished on treatment switching	9.078	8.838	0.239	58,682	52,450	6232	26,052
UKPDS creep for 5 years	8.815	8.571	0.244	62,112	56,011	6101	24,963
Treatment switch after 7 years	9.253	8.844	0.409	58,948	52,236	6712	16,410
Treatment switch after 3 years	9.210	8.829	0.381	54,015	52,620	1395	3667
26-week data	9.212	8.868	0.344	56,861	52,387	4474	13,022

N.B: ICERs calculated based on the incremental costs and quality-adjusted life expectancy values shown in the table differ from the ICER shown in the final column of the table due to rounding
BMI body mass index, *EUR* 2012 Euros, *HbA1c* glycated hemoglobin, *ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life year, *SBP* systolic blood pressure, *UKPDS* United Kingdom Prospective Diabetes Study

116,534 per QALY gained. This was primarily due to the improvements in physiological parameters associated with liraglutide resulting in reduced risk of long-term complications, with the benefits of this not fully realized over shorter time horizons. Changing the discount

rate to 5% led to an increased ICER of EUR 14,955 per QALY gained, and applying a discount rate of 0% led to the ICER falling to EUR 5251 per QALY gained. This pattern also reflects the long-term benefits associated with liraglutide over sitagliptin. Abolishing the treatment effects in turn identified that the key driver of improved health outcomes with liraglutide was the improvement in HbA1c. When this difference was abolished (i.e., the change was assumed to be the same as in the sitagliptin arm) the incremental quality-adjusted life expectancy benefit fell from 0.40 QALYs to 0.10 QALYs. Using alternative assumptions around the long-term progression of HbA1c also resulted in changes in the cost-effectiveness outcomes, but in both cases the ICER remained below EUR 30,000 per QALY gained. Cost-effectiveness outcomes remained stable when the costs of complications were varied, when treatment switching was assumed to take place earlier or later, and when the 26-week trial data were used.

Secondary Analysis

In the secondary analysis, receiving sitagliptin for 1 year followed by liraglutide 1.8 mg therapy for 4 years was associated with increased life expectancy (by 0.23 years) and quality-adjusted life expectancy (by 0.26 QALYs) compared with sitagliptin therapy for 5 years (with patients in both arms of the modeling analysis receiving glargine after year five for the remainder of their lifetime). As in the base case analysis, improvements were driven by a reduced incidence and increased time to onset of diabetes-related complications. Mean costs over patient lifetimes were found to be higher in the delayed liraglutide arm (EUR 56,008 versus EUR 52,450), driven by the acquisition cost of liraglutide in years 2–4 of the analysis. Based on these cost and clinical outcomes, delayed liraglutide therapy was associated with an ICER of EUR 13,628 per QALY gained versus sitagliptin.

Sensitivity analyses showed the same patterns as in the primary analysis. Analyses identified that the key driver of cost-effectiveness was the HbA1c improvement seen when patients switched from sitagliptin to liraglutide at the end of the first year of the analysis. Switching patients to liraglutide was found to be cost-effective as a result of a reduced incidence of diabetes-related complications over the long term, as shown by the analyses in which the time horizon and discount rates were changed.

DISCUSSION

A previous cost-effectiveness analysis in the Spanish setting has suggested that liraglutide 1.2 mg is a cost-effective treatment option, versus sitagliptin, for patients with type 2 diabetes not achieving glycemic control on metformin monotherapy [20]. The present analysis has aimed to expand on the previously published work, by investigating the cost-effectiveness of liraglutide 1.8 mg in Spain based on the 52-week trial data. It was found that liraglutide 1.8 mg was associated with improved life expectancy and quality-adjusted life expectancy compared with sitagliptin in the Spanish setting. Clinical improvements resulted from a reduced incidence and increased time to onset of diabetes-related complications, driven predominantly by a greater reduction in HbA1c, but changes in systolic blood pressure, serum lipid levels and BMI were also found to be important. Liraglutide was associated with an increase in direct medical costs over patient lifetimes. This resulted from the increased

acquisition cost of liraglutide over the short term, but was partially offset by avoidance of treatment of diabetes-related complications over the long term. Based on the projected outcomes, liraglutide 1.8 mg was associated with an ICER of EUR 10,436 versus sitagliptin in the Spanish setting for patients with type 2 diabetes not achieving glycemic targets on metformin monotherapy. This ICER falls below the commonly quoted willingness to pay threshold of EUR 30,000 per QALY gained [29–31], and therefore liraglutide 1.8 mg is likely to be considered a cost-effective treatment option in patients failing to meet glycemic targets on metformin monotherapy.

In the 1860-LIRA-DPP-4 study, the 1.8 mg dose was associated with greater reductions in HbA1c, blood pressure, and BMI at both 26- and 52-week time points than liraglutide 1.2 mg [25, 26]. Whilst care should be taken when results of the previous cost-effectiveness analysis and the present analysis are compared due to the different time points from which data were taken, these studies suggest that the greater improvements in surrogate outcomes with the 1.8 mg dose are likely to result in greater improvements in long-term clinical outcomes and both the 1.2 and 1.8 mg doses of liraglutide are likely to be cost-effective versus sitagliptin in the Spanish setting.

The secondary analysis represents a scenario in which liraglutide therapy is delayed by 1 year, with a year of sitagliptin treatment received previously. This analysis suggested that switching patients from sitagliptin to liraglutide was also a cost-effective treatment strategy for patients failing to meet glycemic targets on metformin monotherapy, compared to remaining on sitagliptin. As in the base case analysis, cost-effectiveness was driven by improvements in HbA1c and BMI when switching from DPP-4 to GLP-1 receptor agonist treatment. However, improvements in risk factors were not as large as when liraglutide 1.8 mg was initiated in the first year of the analysis. Therefore, the gains in life expectancy and quality-adjusted life expectancy were smaller in the secondary analysis of delayed liraglutide therapy than in the base case analysis in which liraglutide was initiated earlier. Furthermore, the ICER in the secondary was higher than in the base case analysis. This suggests that the best strategy for optimizing healthcare outcomes with a limited budget may be to initiate liraglutide earlier rather than later, as this resulted in improved health outcomes at a lower ICER.

As with all scientific studies, the limitations must be considered to put the results into context. A potential limitation of the present study (and also the previous analysis) is that all parts of the 1860-LIRA-DPP-4 study were open label. This included the initial treatment period used in the base case analysis and the extension used to inform the secondary analysis. Open label studies are less robust than double-blind trials, as patients may have expectations of the effects of the study medications and this may influence adherence to lifestyle recommendations. However, the impact of any potential effect is difficult to assess. The impact of this on the present study has been minimized by only using trial endpoints measured through objective tests (such as HbA1c and systolic blood pressure).

A further limitation of the present analysis may be the projection of long-term clinical events based on short-term trials measuring changes in surrogate outcomes. However, this limitation is applicable to the majority of health economic evaluations. Despite this, long-term modeling represents one of the best available options for making estimates of long-term clinical and economic outcomes in the absence of long-term clinical data, and this approach is recommended in guidelines [32]. The present study aims to minimize this limitation, through use of a recently validated model to conduct the analysis, and basing changes in physiological parameters on data collected in a randomized controlled trial [22, 23].

A key study in informing both the effectiveness and cost-effectiveness of diabetes medications in patients failing metformin therapy will be the Glycemia Reduction Approaches in Diabetes [(GRADE) NCT01794143] study, due to report in 2020 [33]. Patients will be randomly assigned to one of four diabetes medications (liraglutide, sitagliptin, glimepiride, and insulin glargine) and followed for 7 years. When this study is complete it will provide a large amount of clinical effectiveness data, and will form a key data source for future economic evaluation when the study reports in 2020.

A potential weakness of the secondary analysis is that treatment effects are taken from different time points, with the sitagliptin treatment arm informed by the 52-week data and the delayed liraglutide treatment arm informed by 52- and 78-week data. It was not possible to use equivalent time point data as all patients that received sitagliptin as part of the 1860-LIRA-DPP-4 trial were switched to liraglutide at 52 weeks. This is unlikely to have had a significant impact on the analysis, as in the 1860-LIRA-DPP-4 study the majority of change in measured outcomes when initiating sitagliptin (or liraglutide) occurred over the first 12 weeks, after which measured values remained stable up to 52 weeks [25, 26].

The impact of adherence to the two diabetes medications evaluated should also be considered. It has been suggested that injectable diabetes medications may be associated with lower adherence than oral medications as a result of the method of delivery [34]. However, it has also been proposed that the favorable clinical profile of incretin therapies, in terms of low hypoglycemic event rates and weight loss, may result in improved adherence compared to conventional diabetes treatments [35]. Whilst adherence to alternative GLP-1 receptor agonists has been assessed, currently there is no evidence to suggest that injectable GLP-1 receptor agonists are associated with lower adherence rates than oral DPP-4 inhibitors [36, 37]. Moreover, the impact of adherence on cost-effectiveness is difficult to assess, as both clinical outcomes and costs will be affected by adherence rates. The conclusions of the present analysis may only be valid for patients who are adherent to the diabetes medications received.

In conclusion, clinical trials have shown that both liraglutide and sitagliptin are effective treatments for patients not achieving glycemic targets on metformin monotherapy. In the recently published 1860-LIRA-DPP-4 trial, liraglutide 1.8 mg was associated with greater improvements in HbA1c and BMI than sitagliptin [25, 26]. Projecting these outcomes over patient lifetimes using a published and validated cost-effectiveness model suggested that liraglutide 1.8 mg is likely to be cost-effective versus sitagliptin in the Spanish setting for patients failing to meet glycemic targets on metformin monotherapy. The secondary analysis suggests that initiating liraglutide earlier, rather than after a year of sitagliptin therapy first, is the optimum method for maximizing health outcomes and cost-effectiveness. The results of the previous and present analyses suggest that both the 1.2 and 1.8 mg doses of liraglutide are likely to be cost-effective for patients with type 2 diabetes not achieving glycemic targets on metformin monotherapy from a healthcare payer perspective in Spain.

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Conflict of interest. Antonio Pérez is a scientific collaborator with Novo Nordisk and has participated in advisory boards and clinical trials. Pedro Mezquita Raya is a scientific collaborator with Novo Nordisk and has participated in advisory boards and clinical trials. Antonio Ramírez de Arellano is an employee of Novo Nordisk. Teresa Briones is an employee of Novo Nordisk. Barnaby Hunt is an employee of Ossian Health Economics and Communications, which received a consulting fee from Novo Nordisk to support the study. William Valentine is an employee of Ossian Health Economics and Communications, which received a consulting fee from Novo Nordisk to support the study.

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ORIGINAL RESEARCH

Cost-Effectiveness of Continuous Subcutaneous Insulin Infusion Versus Multiple Daily Injections in Patients with Poorly Controlled Type 2 Diabetes in Finland

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ABSTRACT

Introduction: Although primarily utilized in type 1 diabetes, continuous subcutaneous insulin infusion (CSII) represents a useful treatment alternative for patients with type 2 diabetes who are unable to achieve good glycemic control despite optimization of multiple daily injections (MDI). The aim of the analysis reported here was to investigate the long-term cost-effectiveness of CSII versus MDI in type 2 diabetes patients with poor glycemic control in Finland.

Methods: The IQVIA CORE Diabetes Model was used to make long-term projections of the clinical and economic outcomes associated with CSII use in type 2 diabetes, based on clinical input data from the OpT2mise trial, which showed that CSII was associated with a 1.1% decrease in glycated hemoglobin (HbA1c) in patients with poor glycemic control at baseline. The analysis was performed from a societal perspective and the time horizon was that of patient lifetimes. Future costs and clinical outcomes were discounted at 3% per annum.

Results: Continuous subcutaneous insulin infusion was associated with a gain in quality-adjusted life expectancy of 0.32 quality-adjusted life-years (QALYs) compared with MDI (8.15 vs. 7.83 QALYs, respectively), as well as higher mean lifetime costs, resulting in an incremental cost-effectiveness ratio of Euro (EUR) 47,834 per QALY gained for CSII versus MDI. The higher treatment costs in the CSII group were partly mitigated by a 15% reduction in diabetes-related complication costs. Sensitivity analyses demonstrated that CSII was most cost-effective in patients with the highest baseline HbA1c values.

Conclusion: In Finland, CSII is likely to represent a cost-effective treatment alternative for patients with type 2 diabetes with poor glycemic control despite optimization of MDI. In such patients, CSII is associated with improved clinical outcomes relative to MDI, with the higher acquisition costs partly offset by a lower lifetime incidence and cost of diabetes-related complications.

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Keywords: Continuous subcutaneous insulin infusion; Cost-effectiveness; Finland; Type 2 diabetes

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INTRODUCTION

In Finland the prevalence of type 2 diabetes has increased considerably in recent years, with figures from the Finnish Diabetes Association estimating that there are currently approximately 300,000 people diagnosed with type 2 diabetes in Finland with a further 150,000 people with undiagnosed diabetes [1]. This high, and increasing, prevalence means that the clinical and economic burden associated with the management of type 2 diabetes is both substantial and growing. The healthcare system in Finland provides universal coverage, although this is largely organized on a municipal rather than national level, resulting is some variation in resource allocation between different municipalities [2]. Treatment for diabetes (including insulin, insulin pens, insulin pumps and self-monitoring of blood glucose strips) is generally fully reimbursed in Finland [3], and it estimated that the management of diabetes and related complications now accounts for 12–15% of total healthcare spending in Finland [4, 5]. Moreover, approximately 90% of the direct medical costs associated with diabetes are attributable to the management of diabetes-related complications, with annual direct costs for type 2 diabetes patients with diabetes-related complications being approximately 20-fold higher than for patients without complications [4]. Macrovascular complications in particular are the leading cause of morbidity and mortality in diabetes patients [5], and these complications account for a substantial proportion of overall healthcare resource utilization [4, 5]. For example, in Finland in 2002 it was estimated that 25% of all myocardial infarctions and additionally 54–60% of all lower limb amputations occurred in people with diabetes [6].

One of the key risk factors for diabetes-related complications is poor glycemic control [7, 8]; consequently, the management of blood glucose levels represents a fundamental component of diabetes management. However, as type 2 diabetes is a progressive disease, achieving glycemic control targets typically requires intensification of treatment as the disease progresses, with patients initiating insulin treatment when target glycated hemoglobin (HbA1c) levels can no longer be achieved with lifestyle modifications and oral antidiabetic (OAD) agents and/or glucagon-like peptide-1 receptor agonists. However, some patients on multiple daily injections (MDI) of insulin remain unable to achieve good glycemic control despite optimization of the insulin regimen [9]. For these patients continuous subcutaneous insulin infusion (CSII; insulin pump) may provide a solution in terms of achieving HbA1c targets.

CSII is frequently used in patients with type 1 diabetes, where it has been shown to improve glycemic control and reduce the risk for severe and nocturnal hypoglycemic events [10, 11]; however, the role of CSII in type 2 diabetes is less well established. The recently published OpT2mise trial was one of the first large-scale, randomized, controlled trials to assess the efficacy and safety of CSII in patients with type 2 diabetes who were unable to achieve good glycemic control despite optimization of MDI of a basal–bolus regimen [12, 13]. At baseline, mean daily basal (long-acting) insulin use in the MDI arm was 52 U/day and the mean daily bolus (rapid-acting) insulin dose was 54 U/day; the corresponding values in the CSII arm were 57 and 56 U/day, respectively. Patients in the OpT2mise trial had a mean baseline HbA1c of 9.0% (75 mmol/mol). At 6 months, CSII-treated patients had significantly greater improvements in glycemic control compared with those that remained on MDI (reduction of 1.1% for CSII vs. 0.4% for MDI) as well demonstrating a clinically significant reduction in the amount of time spent in hyperglycemia [12]. Further, the improvement in HbA1c reported in the CSII group was also sustained through to 12 months [13]. Additionally, Finnish guidelines note that CSII is a treatment option for type 2 diabetes patients treated with insulin [5]. It is estimated that approximately 70% of patients on MDI regimens do not inject insulin outside of the home [14]. This in turn can influence glycemic control, with one study reporting that missing as few as two injections per week can increase the HbA1c level by $\geq$ 0.2% [15]. The flexibility provided by CSII may therefore offer benefits to patients who struggle to manage blood glucose levels with MDI. However, despite these potential benefits, higher initial acquisition costs and a requirement for training can represent barriers to CSII use in type 2 diabetes patients. Although different CSII devices are available from different manufacturers and there are differences in acquisition costs between different devices, the initial cost remains a barrier across all devices.

A long-term cost-effectiveness analysis enables evaluation of whether the higher treatment costs are mitigated by improved glycemic control and the resultant reduction in risk for long-term complications, which are frequently associated with high direct medical costs. As such, the aim of the current analysis was to investigate the long-term clinical and economic outcomes associated with the use of CSII [specifically the MiniMed™ 640G device (Medtronic, Northridge, CA, USA)] compared with MDI in type 2 diabetes patients with poor baseline glycemic control in Finland.

METHODS

Cost-Effectiveness Model Description

The analysis was performed using the IQVIA CORE Diabetes Model ICDM (IQVIA, Basel, Switzerland), which is a validated long-term cost-effectiveness model that can be utilized for analyses of either type 1 or type 2 diabetes [16–18]. Structurally, it is based on a series of inter-dependent sub-models that simulate diabetes-related complications, including long-term cardiovascular, ophthalmic and renal complications; peripheral vascular disease, neuropathy and diabetic foot complications; and acute events, including hypoglycemic events. The sub-models have a semi-Markov structure and use time-, state-, time-in-state- and diabetes type-dependent probabilities derived from published literature to simulate disease progression. Monte Carlo simulation using tracker variables is used to overcome the memoryless properties of a standard Markov model and allows for interconnectivity and interaction between the different sub-models. For each model simulation a cohort of 1000 simulated patients was run through the model using first-order Monte Carlo simulation.

Simulation Cohort and Treatment Effects

Patient characteristics and treatment effects for the simulated cohort were sourced from the OpT2mise study (Table 1). Full details of the OpT2mise trial have been published by Reznik et al. [12]. In OpT2mise, at baseline, the mean (standard deviation; SD) age was 56 (9.6) years, mean (SD) duration of diabetes was 15 (8) years and the mean (SD) HbA1c at baseline was 9.0% (0.75%) (75 [SD 8] mmol/mol). In terms of treatment effects, at month 6 of the OpT2mise

Table 1 Baseline cohort characteristics

Baseline cohort characteristics	Mean (SD)
Age (years)	56 (9.6)
Male (%)	54.4
Duration of diabetes (years)	15 (8)
HbA1c (%)	9.0 (0.75)
Systolic blood pressure (mmHg)	132 (15)
Total cholesterol (mg/dL)	172
High-density lipoprotein (mg/dL)	50
Low-density lipoprotein (mg/dL)	85
Triglycerides (mg/dL)	186
Body mass index (kg/m^2)	33.4 (7.25)
eGFR (mL/min/1.73 m^2)	77.5
Smokers (%)	15

Source: Reznik et al. [12]
eGFR estimated glomerular filtration rate, *HbA1c* glycated hemoglobin, *SD* standard deviation

Table 3 Summary of base case results

Base case results	CSII arm	MDI arm	Difference
Discounted life expectancy (years)	14.41	14.07	0.34
Quality-adjusted life expectancy (QALYs)	8.15	7.83	0.32
Total cost, direct and indirect (EUR)	133,259	118,053	15,206
Total cost, direct costs only (EUR)	104,145	86,865	17,280
Treatment	52,518	26,425	26,093
Management	10,124	9935	189
Cardiovascular disease	8633	8743	− 110
Renal disease	12,053	17,829	− 5776
Ulcer/amputation/neuropathy	2705	2832	− 127
Ophthalmic complications	18,097	20,478	− 2381
Hypoglycemia	0	607	− 607
Depression	15	15	0
ICER (EUR per QALY gained)	47,834		

CSII continuous subcutaneous insulin infusion, *ICER* incremental cost-effectiveness ratio, *MDI* multiple daily injections, *QALY* quality-adjusted life-year

EUR 47,834 per QALY gained for CSII versus MDI.

Higher total costs in the CSII arm were primarily driven by higher treatment costs associated with CSII use, with lifetime treatment costs being EUR 26,093 higher in the CSII arm than in MDI arm. However, this was partially offset by lower complication costs in the CSII arm; overall, over patient lifetimes mean complication costs were 15% lower in the CSII arm than in the MDI arm. In particular, mean total renal and ophthalmic complication costs were lower in the CSII arm compared with the MDI arm by more than EUR 5000 and EUR 2000, respectively. The lower complication costs in the CSII arm were driven by improved glycemic control leading to a delay in both the onset and lower cumulative incidence of diabetes-related complications in the CSII arm (Fig. 1). For example, the use of CSII was associated with mean delay in onset of > 1 year for several complications, including retinopathy, proteinuria, neuropathy and macula edema.

The base case analysis included indirect costs associated with lost productivity; however, when only direct costs were included the ICER increased slightly to EUR 54,358 per QALY gained. The findings from other sensitivity analyses show that the cost-effectiveness of CSII was strongly associated with baseline HbA1c, the acquisition cost of CSII and the time horizon (Table 4). Sensitivity analyses around baseline HbA1c showed that CSII was most cost-effective in those patients with the poorest glycemic control at baseline; in a scenario in which mean baseline HbA1c was increased to 9.5% the ICER for CSII versus MDI decreased to EUR 25,555 per QALY gained. In contrast, if the mean baseline HbA1c was decreased to 8.5% the ICER increased to EUR 129,016 per QALY gained. Sensitivity analyses around the cost of CSII showed that, as anticipated, a 20% reduction in CSII acquisition cost led to an ICER of EUR 23,420 per QALY gained while a 10% increase in CSII cost resulted in the ICER increasing to EUR 60,041 per QALY gained. The results were also sensitive to changes in the time horizon of the analysis; over a short time horizon (5 years) the ICER increased to EUR 310,271 per QALY gained, likely due to the fact that the

Table 2 Treatment/management costs for diabetes-related complications

Event	Cost (in Euro)	References
Myocardial infarction, year of event	5187	Sabale et al. [19]
Myocardial infarction, subsequent years	122	Sabale et al. [19]
Angina, first year	3802	Sabale et al. [19]
Angina, subsequent years	169	Sabale et al. [19]
Congestive heart failure, first year	4186	Sabale et al. [19]
Congestive heart failure, subsequent years	396	Sabale et al. [19]
Stroke, year of event	6073	Sabale et al. [19]
Stroke, subsequent years	256	Sabale et al. [19]
Stroke death within 30 days	5907	Sabale et al. [19]
Peripheral vascular disease, annual	3344	DRG cost [20]
Hemodialysis, annual	55,370	Sabale et al. [19]
Peritoneal dialysis, annual	55,370	Sabale et al. [19]
Renal transplant, year of event	57,770	DRG cost [20]
Renal transplant, subsequent years	1955	DRG cost [20]
Major hypoglycemic event	3374	DRG cost [20]
Lactic acid event	3405	DRG cost [20]
Edema, onset	2996	DRG cost [20]
Edema, follow-up	258	DRG cost [20]
Photocoagulation	2864	DRG cost [20]
Cataract operation	798	DRG cost [20]
Cataract follow-up	445	DRG cost [20]
Blindness, year of onset	14,694	Sabale et al. [19]
Blindness, subsequent years	469	Schwarz et al. [21]
Neuropathy, annual	271	DRG cost [20]
Amputation, event	10,118	Sabale et al. [19]
Amputation prosthesis, event based	10,118	Sabale et al. [19]
Gangrene treatment	3854	DRG cost [20]
After healed ulcer	273	DRG cost [20]
Infected ulcer	2157	DRG cost [20]
Standard uninfected ulcer	273	DRG cost [20]
Healed ulcer, history of amputation	165	Sabale et al. [19]

All costs are presented in 2017 Euro
DRG Diagnosis-related group

trial, patients on CSII has a mean reduction from baseline in HbA1c of − 1.1% compared with − 0.4% for patients in the MDI arm. Additionally, in the CSII arm there were no major hypoglycemic events compared with an event rate of 1.2 events per 100 patient-years in the MDI arm.

Costs and Utilities

In terms of intervention costs, only the incremental cost of CSII relative to MDI was included in the analysis (i.e. the cost difference between the CSII and MDI arms). Incremental treatment costs for the CSII arm included the acquisition cost of a MiniMed 640G™ insulin pump (Medtronic) and its consumables (infusion sets and reservoirs), as well as the cost of pump initiation training and the difference between the two arms in terms of insulin costs, as well as pens and needles. Direct medical costs for diabetes-related complications were sourced from published literature [19–21] (Table 2) and, where necessary, inflated to 2017 Euro (EUR) using the consumer price index from Statistics Finland [22]. Indirect costs associated with lost productivity were based on the human capital approach; age at first income, retirement age and average salaries were sourced from Statistics Finland [23]. In the absence of data specific to Finland, the duration of absenteeism from work owing to diabetes-related complications was sourced from a 2013 analysis from Denmark by Sørensen and Ploug [24]. Health state utility values (specific to patients with type 2 diabetes) for diabetes-related complications were sourced from a review by Beaudet et al. [25].

Discount Rate, Time Horizon and Perspective

The base case analysis was performed from the societal perspective (a sensitivity analysis was performed in which only direct costs were included). Future costs and clinical outcomes were discounted at a rate of 3% per annum in line with Finnish guidelines [26], and the time horizon of the analysis was that of patient lifetimes.

Sensitivity Analysis

A series of one-way sensitivity analyses were performed to determine the key drivers of outcomes. In particular, the influence of baseline HbA1c on outcomes was assessed by increasing and decreasing mean baseline HbA1c to 8.5% (69 mmol/mol) and 9.5% (80 mmol/mol), respectively (compared with 9.0% [75 mmol/mol] in the base case analysis). The influence of the acquisition cost of CSII was assessed by performing analyses in which the cost of the pump, infusion set and reservoir were decreased by 10 and 20%, respectively, and increased by 10%. Allied to this, sensitivity analyses were performed in which the costs of diabetes-related complications were increased and decreased by 20% relative to the base case.

The influence of time horizon and discount rates on outcomes was also assessed. Sensitivity analyses were performed over time horizons of 5, 10 and 20 years, and analyses were run using discount rates of 0 and 5% per annum.

Compliance with Ethics Guidelines

This article does not contain any studies with human participants or animals performed by any of the authors.

RESULTS

In the base case analysis, the use of CSII was associated with higher life expectancy and quality-adjusted life expectancy relative to MDI (Table 3). In the CSII group the projected mean quality adjusted life expectancy was 8.15 quality-adjusted life-years (QALYs) compared with 7.83 QALYs in the MDI group (difference of 0.32 QALYs). Similarly, discounted life expectancy was 0.34 years higher in the CSII arm than in the MDI arm (14.41 vs. 14.07 years, respectively). However, overall mean total lifetime costs were EUR 15,206 higher in the CSII group than in the MDI group (EUR 133,259 vs. EUR 118,053, respectively), resulting in an incremental cost-effectiveness ratio (ICER) of

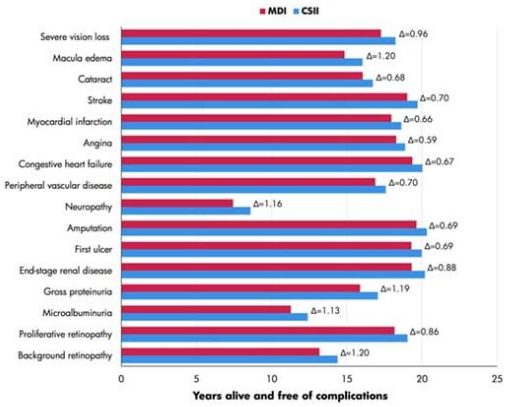

Fig. 1 Time alive and free of diabetes-related complications. *CSII* Continuous subcutaneous insulin infusion, *MDI* multiple daily injections

reduction in long-term complications associated with CSII use may not be apparent over such a short time horizon.

DISCUSSION

The results of the analysis suggest that, in Finland, for type 2 diabetes patients failing to achieve good glycemic control on MDI, switching to CSII is likely to be associated with improved clinical outcomes and over a long-term time horizon is likely to be cost-effective compared with remaining on MDI. In the base case analysis, the ICER for CSII versus MDI was below the commonly cited willingness-to-pay threshold of EUR 50,000 per QALY gained, suggesting that in the long-term, CSII would likely represent a cost-effective treatment option for patients with type 2 diabetes who cannot achieve good glycemic control on MDI. Moreover, sensitivity analyses demonstrated that long-term clinical and economic benefits were most pronounced in patients with the poorest glycemic control at baseline, with the ICER falling to below EUR 30,000 per QALY gained for patients with a baseline HbA1c of 9.5%. This finding is in line with a recent post hoc analysis of 6-month data from the OpT2mise trial, which showed that higher baseline HbA1c was associated with a significantly greater reduction in HbA1c with CSII [27]. Additionally, although recent data are lacking, studies from 2004 to 2005 estimate that in Finland between 8 and 20% of people with type 2 diabetes had a HbA1c > 9%, although the proportion of poorly controlled patients on MDI versus those on OAD agents or lifestyle intervention alone is unknown [6]. Taken together, these findings suggest that insulin-treated type 2 diabetes patients with HbA1c values of ≥ 9.5% would derive the greatest clinical benefit from switching to CSII and that this would be a cost-effective treatment modality from a payer perspective as well.

These findings largely concur with previous health economic analyses from the Netherlands and the USA. In the Netherlands, a 2016 analysis that also utilized clinical input data from the OpT2mise trial reported an ICER (from a third-party payer perspective) of EUR 62,895 per QALY gained [28]. Similarly, a real-world USA-based analysis from 2010 reported that for poorly controlled type 2 diabetes patients, total costs over a 4-year period were influenced by basal insulin dose at baseline and the effect of switching to CSII on the daily insulin dose. In patients with basal insulin use of < 100 U/day at baseline, CSII was associated with an incremental cost of USD 5822 versus MDI over the 4-year period. However, in those with baseline basal insulin use of > 150 U/day, CSII was found to be cost-saving compared with MDI over 4 years [29].

Although the management of patients with type 2 diabetes is multifactorial, maintaining good glycemic control is a key component of disease management. It is well established that elevated HbA1c is a key risk factor for diabetes-related complications and mortality [30, 31]. In this analysis, the improved glycemic control in the CSII arm relative to the MDI arm is therefore likely to have been a key driver of the projected lower cumulative incidence of complications in the CSII arm. In the OpT2mise trial the CSII arm experienced a HbA1c reduction of − 1.1% compared with − 0.4% for patients in the MDI arm. This treatment effect is consistent with the findings of earlier smaller trials as well as a recent meta-analysis of a total of five randomized controlled trials [32–35]. For example, in one small-scale study from France, type 2 diabetes patients with a mean baseline HbA1c of 9.0% (75 mmol/mol) experienced a significantly greater improvement with CSII than with MDI ($p < 0.03$), with the magnitude of the treatment effect in terms of CSII similar to that reported in the OpT2mise trial [32]. Similarly, a 2017 meta-analysis, which included individual patient-level data from a total of 287 patients on MDI and 303 on CSII, showed that overall compared with MDI, CSII was associated with a HbA1c reduction of 0.4% (4.4 mmol/mol), although this treatment effect was much greater in patients with the poorest glycemic control at baseline [35]. This finding lends further weight to the hypothesis that those patients with the poorest glycemic control at baseline may represent the group that derives the largest clinical benefit from switching to CSII. The authors of the 2017 meta-analysis also report that across the five trials included in their meta-analysis CSII was associated with a 26% reduction in insulin dose, with the largest reduction being reported in those patients with the highest insulin doses at baseline [35]. In addition to data from clinical trials, USA-based data from routine clinical practice show that for type 2 diabetes patients who fail to achieve glycemic control by MDI, switching to CSII was associated with improved glycemic control in addition to a reduced incidence of emergency room visits and inpatient admissions [36, 37].

The current analysis is associated with limitations. In particular, long-term complication rates have been projected on the basis of the 6-month findings from a single clinical trial. However, long-term, large-scale data relating to the use of CSII in type 2 diabetes, either from clinical trials or real-world studies, are lacking, although data from a study in 102 patients in France showed that the treatment effect in terms of improved HbA1c persisted throughout 6 years of follow-up [38]. Nevertheless, the OpT2mise trial represents the largest trial of CSII in type 2 diabetes conducted to date and, therefore, despite the short-term nature of the trial, it is likely the most robust source of clinical evidence available for projecting long-term clinical and economic outcomes. Additionally, in the absence of data specific to Finland, it was necessary to utilize data from Denmark in relation to absenteeism related to diabetes-related complications. These data may not be fully generalizable to Finland owing to differences in social security or sickness benefit systems between settings.

Table 4 Summary findings of sensitivity analyses

Sensitivity analyses	CSII arm		MDI arm		ICER (EUR per QALY gained)
	Total costs (EUR)	QALYs	Total costs (EUR)	QALYs	
Base case	133,259	8.151	118,053	7.833	47,834
Direct costs only	104,145	8.151	86,865	7.833	54,358
CSII costs: − 20%	125,498	8.151	118,053	7.833	23,420
CSII costs: − 10%	129,379	8.151	118,053	7.833	35,627
CSII costs: + 10%	137,140	8.151	118,053	7.833	60,041
Baseline HbA1c: 8.5%	132,697	8.180	111,964	8.019	129,016
Baseline HbA1c: 9.5%	135,150	8.094	124,169	7.664	25,555
Complication costs: + 20%	145,870	8.151	132,354	7.833	42,515
Complication costs: − 20%	124,460	8.151	107,444	7.833	53,529
Time horizon: 5 years	36,286	2.783	29,956	2.762	310,271
Time horizon: 10 years	71,171	4.841	61,306	4.761	123,930
Time horizon: 20 years	106,210	7.179	92,263	6.994	75,389
0% per annum discount rate	199,245	11.368	178,048	10.808	37,831
5% per annum discount rate	106,694	6.759	93,945	6.530	55,695

CSII continuous subcutaneous insulin infusion, *ICER* incremental cost-effectiveness ratio, *MDI* multiple daily injections, *QALY* quality-adjusted life years

CONCLUSION

The findings of this cost-effectiveness analysis, which is based on clinical input data from the OpT2mise trial, suggest that in Finland, CSII is likely to be cost-effective for patients unable to achieve good glycemic control on MDI. Further, our sensitivity analyses suggest that CSII is most cost-effective in those with the poorest glycemic control at baseline. The projected improvements in glycemic control with CSII were in turn projected to translate into a lower incidence of long-term diabetes-related complications, which partly offsets the higher treatment costs of CSII. As such, in Finland, based on a willingness-to-pay threshold of EUR 50,000 per QALY gained, switching to CSII using the MiniMed™ 640G device is likely to be good value for money for type 2 diabetes patients on MDI with HbA1c levels of > 9.0%.

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Compliance with Ethics Guidelines. This article does not contain any studies with human participants or animals performed by any of the authors.

Data Availability. The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Cost Effectiveness and Resource Allocation

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Insulin glargine compared to neutral protamine Hagedorn (NPH) insulin in patients with type-2 diabetes uncontrolled with oral anti-diabetic agents alone in Hong Kong: a cost-effectiveness analysis

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Abstract

Background: International guidelines recommend using basal insulin in patients with type-2 diabetes mellitus if glycaemic target cannot be attained on non-insulin anti-diabetic drugs. Available choices of basal insulin include intermediate-acting neutral protamine Hagedorn (NPH) insulin and long-acting insulin analogues like insulin glargine U100. Despite clear advantages of glargine U100, the existing practice in Hong Kong still favours NPH insulin due to lower immediate drug costs.

Objectives: The objective of this study was to assess the cost-effectiveness of insulin glargine U100 compared to NPH insulin in patients with type-2 diabetes uncontrolled with non-insulin anti-diabetic agents alone in Hong Kong.

Methods: The IQVIA™ Core Diabetes Model (CDM) v9.0 was used to conduct the cost-effectiveness analysis of glargine U100 versus NPH. Baseline characteristics were collected from the Hong Kong Diabetes Registry. Efficacy rates were extracted from a published study comparing glargine U100 and NPH in Asia, utilities from published literature, and costs constructed using the Hong Kong Hospital Authority (HA) Gazette (public healthcare setting). The primary outcome was an incremental cost-effectiveness ratio (ICER).

Results: Insulin glargine U100 resulted in an ICER of HKD 98,663 per Quality Adjusted Life Year (QALY) gained. The incremental gains in QALY and costs were 0.217 years and HKD 21,360 respectively. Results from scenario and probabilistic sensitivity analyses were consistent with that from base case analysis.

Conclusion: Insulin glargine U100 is a cost-effective treatment for patients with type 2 diabetes compared to NPH insulin in setting in Hong Kong. This was mainly driven by the significantly lower rates of hypoglycaemia of insulin glargine U100 than NPH insulin.

Keywords: Cost-effectiveness, Glargine U100, Neutral protamine Hagedorn (NPH), Type 2 diabetes mellitus (T2DM), CORE Diabetes Model (CDM)

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Background

Type 2 diabetes mellitus is a chronic medical condition characterised by inadequate insulin production and action resulting in hyperglycaemia. People with diabetes are at risk of developing micro-/macrovascular complications of serious consequences particularly if glycaemia and other metabolic risk factors are inadequately managed [1–3]. Maintenance of optimal glycaemic control requires successive up-titration of anti-diabetic medications and insulin supplement will be required in the majority of patients as pancreatic beta-cell function deteriorates over time [4]. International guidelines recommend initiation of basal insulin if glycaemic target cannot be attained on non-insulin anti-diabetic drugs [5, 6]. The current available choices of basal insulin include intermediate acting neutral protamine Hagedorn (NPH) insulin and the long-acting insulin analogue such as insulin glargine U100. Insulin glargine U100 offers a smooth 24-h time-action profile with no pronounced peak which closely resembles endogenous basal insulin. In clinical studies, glargine U100 had superior or equivalent glucose lowering efficacy but was associated with fewer events of symptomatic or asymptomatic daytime or nocturnal hypoglycaemia in comparison with NPH [7]. Despite clear advantages of long-acting insulin analogues such as glargine U100 over NPH, the existing practice in Hong Kong public healthcare setting still favours NPH due to lower immediate drug costs. On the other hand, the overall cost-effectiveness of a treatment needs to factor in future savings from medical costs related to hospital admissions for complications as well as gain in quality of life. Hong Kong has a heavily subsidised public healthcare system. Given the huge difference in out-of-pocket medical costs between public and private sector, over 80% of people with chronic diseases seek care in public health facilities. In 2016, close to 400,000 individuals with diabetes are receiving medical services in the Hospital Authority, the governing body of all public hospitals and most out-patient clinics in Hong Kong, and the number is expected to rise at 1% per year [8]. Previous cost-effectiveness studies performed in Europe and North America indicated that use of glargine U100 is cost-effective but similar studies have not been conducted in Asia [9, 10]. In the present study, we examined the cost-effectiveness of insulin glargine U100 compared with NPH insulin from a societal perspective in Hong Kong. However, it is worth noting that we consider the value of costs within the public healthcare setting rather than the private setting, since both settings entail different medical costs for the same medical procedures. The efficacy data of glargine U100 versus NPH was based on the results reported in the Lantus evaluation in Asian diabetics (LEAD) study [7], a 24-week randomised controlled study comparing these two insulins on glucose lowering and rates of hypoglycaemia in insulin-naive Asian subjects with type 2 diabetes inadequately controlled on sulphonylurea. The results of the present analysis are intended to add further insights to the existing pharmacoeconomic research in diabetes mellitus specifically in Asia and to support an informed decision to widen the use of insulin glargine U100 in the public setting in Hong Kong which will improve patients' quality of life while relaxing the pressure on the healthcare budget.

Methods

The objective of the current study was to assess the cost-effectiveness of insulin glargine U100 compared to NPH insulin in patients with type-2 diabetes uncontrolled with non-insulin anti-diabetic agents alone in Hong Kong. We took the societal perspective in Hong Kong for this cost-effectiveness analysis. The analysis was conducted using the internet-based computer simulation IQVIA CORE Diabetes Model (CDM) which will be discussed in further details below.

IQVIA™ Core Diabetes Model

The IQVIA™ Core Diabetes Model (CDM) v9.0 was used to predict the lifelong costs and outcomes of using insulin Glargine U100 and NPH insulin in patients uncontrolled on non-oral anti-diabetic drugs. A detailed description of the CDM and its operational features have been published elsewhere [11, 12]. The model is a validated [13] internet based computer simulation that predicts the long-term health outcomes and economic consequences in patients with type 2 diabetes starting from changes in physiological parameters (glycated haemoglobin [HbA1c], blood pressures, lipids, body weight, etc.) using risk equations. The most used set of risk equations was developed based on the United Kingdom Prospective Diabetes study (UKPDS) [14, 15]. In addition, the CDM contains other risk equations including equations derived from the Hong Kong Diabetes Registry (HKDR) [16, 17] which are more applicable to Asians given that there are inter-ethnic differences in propensity for diabetes complications and their risk determinants. The Hong Kong risk equations were used in the base case analysis.

CDM is often used as a policy analysis tool because it is a non-product specific model. It comprises of a series of 15 sub-models, where each sub-model is a combination of semi-Markov model structures and Monte Carlo simulations, which simulate the major complications of diabetes including, but not limited to, congestive heart failure, myocardial infarction, stroke, end-stage renal disease, lower extremity amputation, foot ulcer and hypoglycaemia. The model uses time, state, and diabetes type-dependent probabilities derived from published sources, in addition to utilizing tracker variables to overcome the "memory-less" properties of standard Markov models. This allows the interconnectivity and interaction between individual complications' sub-models and hence allows the patient cohort to develop multiple complications within each model cycle. The CDM projects the outcomes for the population based on the following non-exhaustive list: the cohort's baseline characteristics, past history of complications, concomitant medications, and changes in physiological variables over time. From there, the model can calculate the incidence of complications, life expectancy, quality-adjusted life expectancy, and total costs within the population. The results are expressed in terms of quality-adjusted life years gained and incremental cost-effectiveness ratio (ICER). An ICER threshold of 343,312 Hong Kong Dollars (HKD) in Hong Kong (2016) was used in this analysis based on the guidance by the World Health Organization (WHO) which recommends an ICER threshold that is equal to the Gross Domestic Product (GDP) per capita [18, 19].

Baseline characteristics of patient cohort

The baseline characteristics for the base case analysis were collected from the HKDR after applying the inclusion criteria of the LEAD study (Table 1). Also, a scenario was created where the original baseline characteristics from the LEAD trial were used. The reason for this is to test the sensitivity of the results to the underlying baseline cohort, where the base case considers a real-setting (HKDR population) and the scenario is based on the clinical trial population (Scenario 1: LEAD study baseline cohort). The HKDR is an open prospective cohort established since 1994 at the Diabetes and Endocrine Centre, Prince of Wales Hospital, Hong Kong. The registry consecutively enrolled patients with type 1 or type 2 diabetes who were referred to the Centre by specialist and family medicine out-patient clinics for comprehensive assessment of metabolic profile and diabetes complications. The Prince of Wales hospital serves approximately 1.3 out of 7.2 million residents in Hong Kong and thus the registry is considered representative of the general Hong Kong diabetes population. From its inception to 31 May 2007, 10,129 patients with type 1 or type 2 diabetes were enrolled. The patient inclusion criteria of the LEAD study was applied to the HKDR to identify Asian-specific baseline characteristics of the base case cohort as follows: (1) type 2 diabetes (2) on non-insulin anti-diabetic drugs and (3) HbA1c ≥ 7.5%. From the registry, 2344 patients with type 2 diabetes met the inclusion criteria, with mean (standard deviation [SD]) diabetes duration of 7.08 (6.46) years, mean HbA1c 8.98 (1.49)%, and microvascular complications in 20–30% at baseline. A summary of the

Table 1 Baseline characteristics of patient cohort from the Hong Kong Diabetes Registry (base case) and the LEAD study (scenario analysis)

	Hong Kong Diabetes Registry	LEAD study
Demographics and metabolic profile		
Age (year)	57.28 ± 13.05	56.1 ± 8.6[a]
Male (%)	49.4	42[a]
Current smoker (%)	16.02	16.02
Duration of diabetes (year)	7.08 ± 6.46	10.4 ± 5.8[a]
HbA1c (%)	8.98 ± 1.49	9.04 ± 0.86[a]
Body mass index (kg/m^2)	25.36 ± 4.04	24.95 ± 3.2[a]
Systolic blood pressure (mmHg)	135.52 ± 20.28	135.52 ± 20.28
Diastolic blood pressure (mmHg)	76.25 ± 10.91	76.25 ± 10.91
Total cholesterol (mg/dL)	207.13 ± 46.51	207.13 ± 46.51
HDL-cholesterol (mg/dL)	49.96 ± 13.13	49.96 ± 13.13
LDL-cholesterol (mg/dL)	123.35 ± 38.85	123.35 ± 38.85
Triglyceride (mg/dL)	183.97 ± 193.81	183.97 ± 193.81
Estimated GFR (mL/min/1.73 m^2)	82.27 ± 22.66	82.27 ± 22.66
Haemoglobin (g/dL)	13.98 ± 1.57	13.98 ± 1.57
White blood cell (10^9/mL)	7.47 ± 2.57	7.47 ± 2.57
uACR[a] [20]	3.1 mg/mmol	3.1 mg/mmol
Serum creatinine[b] [21]	0.946 mg/dL	0.946 mg/dL
Serum albumin[b] [21]	3.9 g/dL	3.9 g/dL
Cigarettes/day[b] [22]	2	2
Alcohol consumption[b] [23]	5 Oz/week	5 Oz/week
Diabetes complications		
Acute myocardial infarction (%)	8.19	8.19
Angina (%)	8.19	8.19
Congestive heart failure (%)	1.83	1.83
Stroke (%)	1.96	1.96
Peripheral vascular disease (%)	5.12	5.12
Atrial fibrillation[b] (%) [24]	0.03	0.03
LVH[b] (%) [25]	0.03	0.03
Microalbuminuria (%)	29.48	29.48
Gross renal proteinuria[b] (%) [26]	0.139	0.139
End-stage renal disease (%)	0.30	0.30
Background diabetic retinopathy (%)	25.06	25.06
Proliferative diabetic retinopathy (%)	2.20	2.20
Sever vision loss[b] (%) [27]	0.079	0.079
Macular edema[b] (%) [27]	0.01	0.01
Cataracts (%)	23.29	23.29
Diabetic neuropathy (%)	22.87	22.87
Amputation (%)	0.26	0.26

Values are expressed as mean (standard deviation) or percentages as appropriate

GFR glomerular filtration rate, *HbA1c* glycated haemoglobin, *HDL* high density-lipoprotein, *LDL* low density-lipoprotein, *LEAD* Lantus evaluation in Asian diabetics, *LVH* left ventricular hypertrophy, *uACR* urinary albumin–creatinine ratio

[a] LEAD study [7]

[b] CDM default value. Source between parenthesis

baseline clinical characteristics of the identified patient cohort is shown in Table 1.

When certain characteristics' values were required in the CDM but were not captured within the registry or the LEAD study, the default values in the CDM were used, which are based on published literature [20–27]. These included smoking and alcohol use, heart rate, urine albumin excretion rate, serum albumin, background prevalence of atrial fibrillation, left ventricular hypertrophy, gross proteinuria, severe vision loss, macular oedema, uninfected ulcer, infected ulcer and healed ulcer (Table 1). Those characteristics with CDM default values are not drivers of the model but were needed for the model to run. The base case analysis was run on a cohort of 1000 patients.

Intervention and comparator

In the current analysis, we compared the intermediate-acting neutral protamine Hagedorn (NPH) insulin (comparator) versus the long-acting insulin analogue insulin glargine U100 (intervention) in patients with T2DM uncontrolled with non-insulin non-diabetic agents alone.

Efficacy rates and health utility

The current analysis compared insulin glargine U100 versus NPH Insulin and the efficacy data of each treatment was taken from the results reported in the LEAD study. In the intention-to-treat analysis, reductions in HbA1c for glargine U100 and NPH were 1.10% and 0.92% respectively and the difference between adjusted mean changes in the two treatment groups was 0.22 ($p = 0.0319$). After the first year, HbA1c was set to increase following the natural progression as defined by the Hong Kong Diabetes Registry risk equation. The rates for non-severe hypoglycaemia used as input were 671.67 and 990 per 100 patient-years for glargine U100 and NPH respectively ($p < 0.004$) (Table 2) while the rates for severe hypoglycaemia were 4.90 per 100 patient-years for glargine U100 and 27.2 per 100 patient-years for NPH ($p < 0.03$) based on the LEAD study. The CDM distinguishes between severe hypoglycaemia that does not require medical assistance (severe hypoglycaemia 1) and one that requires medical assistance (severe hypoglycaemia 2). The proportion of severe hypoglycaemia requiring medical assistance was set at 11.8% as reported by Foos et al. [28]. In addition, the proportion of patients experiencing nocturnal hypoglycaemia was calculated from the results of the LEAD study [7] as 0.324 for the glargine U100 arm versus 0.608 and was used as such in the analysis. However, it was assumed that this proportion was the same for non-severe and severe hypoglycaemia.

Quality of life (QoL) was incorporated into the model through using health utilities. Since there are no QoL data specific to the Chinese population, the research team relied on published literature [29–37] (Table 3) to identify utility values for the health states. The baseline utility for uncomplicated type 2 diabetes is 0.8140 [29] which changes into a lower utility when the patient changes health state or a disutility (i.e. decrease in base utility by a given amount) when the patient experiences complications.

Table 2 Treatment effects of insulin glargine and NPH insulin

Type of hypoglycaemia	Insulin glargine		Insulin NPH	
	Mean	SE	Mean	SE
HbA1c decrease from baseline (%)	−1.1	0.074	−0.92	0.074
Non-severe hypoglycaemia event rate	671.67	–	990.06	–
Severe hypoglycaemia 1 event rate (requiring non-medical assistance)	4.32	–	23.99	–
Severe hypoglycaemia 2 event rate (requiring medical assistance)	0.58	–	3.21	–

Costs

Drug acquisition costs

Drug acquisition costs for insulin Glargine U100 and NPH were based on the purchase prices paid by the HA to the supplier (payer perspective) in 2018. The current cost of insulin glargine U100 was HKD 0.40 per unit, and the cost of insulin glargine U100 was fourfold that of NPH insulin. During the first year, a Drug Daily Dose (DDD) of 32.1 units (glargine U100) and 32.8 units (NPH) was applied which were the doses used in the LEAD trial. The dose for each treatment was then up-titrated in the second year by 10% and remained stable afterwards. It was assumed that there would be no adjustment to non-insulin and anti-diabetic medications throughout the simulation.

Complication costs

Costs of treating diabetes-related complications in 2018 were constructed from the HA Gazette [38] (Table 4) which sets out charges of healthcare services run by the HA. The average of listed prices was used when the costs of certain treatment and investigation items were expected to vary depending on their complexity or scope. For complications that required hospitalization, the median length of in-patient stay was determined using statistics from the HKDR. Furthermore, input from experienced medical specialists was utilized to estimate the requirement of other management and investigational items such as consultations at out-patient clinics.

Table 3 Health-related quality-of-life (QoL) values

Utility or disutility	Mean	References
Uncomplicated type 2 diabetes	0.8140	[29]
Myocardial infarction	0.7360	[29]
Disutility post-myocardial infarction event	−0.1290	[29]
Angina	0.6828	[29]
Congestive heart failure	0.6330	[29]
Stroke	0.5450	[29]
Disutility post-stroke event	−0.2610	[29]
Peripheral vascular disease	0.5700	[30]
Microalbuminuria	0.8140	[29]
Gross proteinuria	0.8140	[29]
Haemodialysis	0.6040	[31]
Peritoneal dialysis	0.6128	[31]
Renal transplant	0.7500	[30]
Background diabetic retinopathy	0.7900	[32]
Proliferative diabetic retinopathy	0.7900	[32]
Macular oedema	0.7900	[32]
Severe vision loss	0.6700	[33]
Cataracts	0.6280	[34]
Diabetic neuropathy	0.6300	[33]
Healed ulcer (no data; assumed same as uncomplicated T2DM)	0.8140	[29]
Active ulcer	0.7500	[35]
Lower limb amputation	0.4028	[29]
Disutility post-amputation	−0.5380	[29]
Disutility for daytime non-severe hypoglycaemic event	−0.0050	[36]
Disutility for nocturnal non-severe hypoglycaemic event	−0.0070	[36]
Disutility for daytime severe hypoglycaemic event not requiring medical assistance	−0.0263	[37]
Disutility for nocturnal severe hypoglycaemic event not requiring medical assistance	−0.0263	[37]
Disutility for daytime severe hypoglycaemic event requiring medical assistance	−0.0550	[36]
Disutility for nocturnal severe hypoglycaemic event requiring medical assistance	−0.0570	[36]

Table 4 lists the costs for managing different diabetes-related complications in the public healthcare setting. The direct costs of non-severe and severe hypoglycaemic events were calculated based on published literature adjusted for local costs [39, 40] (Table 5). For a severe hypoglycaemic event that required non-medical third person assistance, an additional 5.6–6.4 test strips was realized and all patients would attend out-patient clinic for medical review [39, 40]. For a severe hypoglycaemic event that required immediate medical assistance, all patients would attend Accident and Emergency Department and patients would be hospitalised for a median length of 3 days based on statistics from the HKDR (Table 5).

Indirect costs

Within this analysis, we also considered indirect healthcare costs, specifically absenteeism costs. This means that for patients who are absent from work due to diabetes complications, we quantify the economic value of these absent days (Table 6). A diabetic treatment that provides better glycaemic control than its comparator will cause less complication in patients, and hence less days absent from work (i.e. lower indirect costs).

Indirect costs are captured based on the human capital approach, which takes into account the value of lost production resulting from morbidity and mortality associated with the disease for patients of working age.

Costs per day absent from work are calculated separately for males and females based on the average annual salary (for males and females) and the number of working days per year. Each complication is associated with days absent from work and this is assigned to each patient in each year of the simulation.

Table 6 shows the inputs for the indirect costs. The days off work (DoW) were sourced from the medical records of the Prince of Wales Hospital (Hong Kong) which is the hospital where the Hong Kong Diabetes Registry is based.

Table 4 Costs of treatment of diabetes complications per T2DM patient in Hong Kong

Diabetes complication	Year of treatment	Cost (HKD)
Myocardial infarction	Year 1	98,947
	Year 2+	2220
Angina	Year 1	41,567
	Year 2+	2220
Congestive heart failure	Year 1	33,990
	Year 2+	4800
Stroke	Year 1	144,120
	Year 2+	2220
Peripheral vascular disease	Year 1	54,719
	Year 2+	2220
Haemodialysis	Year 1	702,000
	Year 2+	702,000
Peritoneal dialysis	Year 1	102,380
	Year 2+	92,100
Renal transplant	Year 1	307,280
	Year 2+	4440
Laser treatment for the eye	Per event	12,900
Cataract	Per event	39,500
Amputation	Per event	226,830
Amputation prosthesis	Per event	8275
Gangrene	Per event	114,560
After healed ulcer	Per event	20,400
Infected ulcer	Per event	39,680
Standard uninfected ulcer	Per event	7980

The days off work for each complication represent the days of hospitalization for the complication, however this does not take into account days off work after the patient is discharged from the hospital. Therefore, we expect that real indirect costs to be even higher than estimated here. We take a conservative approach since no further data is available on the absent days that the patient needs after hospital discharge due to a diabetes complication. Furthermore, the annual salary was obtained from an annual report published by the Statistics Department of the Hong Kong Government [41].

Time horizon and discounting

A lifetime horizon of 50 years was deemed appropriate and used for this analysis with a 3% discount rate for both costs and outcomes as recommended by the Chinese Center for Health Economics Research [42].

Scenario analysis

Scenario analyses were conducted to test the consistency of results to changes in various input variables (Table 7). Scenario 1 under the current analysis adjusted the baseline characteristics of the patient cohort to be the same as those reported in the LEAD study (Table 1). Differences in baseline clinical features between the two cohorts included lower proportion of male (42% versus 49.4%), longer duration of diabetes (10.3 ± 6.3 years versus 7.08 ± 6.46 years), modestly higher HbA1c (9.04 ± 0.86% versus 8.98 ± 1.49%) and lower BMI (24.95 ± 3.20 kg/m^2 versus 25.36 ± 4.04 kg/m^2) in the LEAD study cohort

Table 5 Direct costs of hypoglycaemic events

Treatment items	Cost per treatment item (HKD)	Number required (minimum)	Number required (maximum)	Cost per event (HKD)
Non-severe hypoglycaemic event				
Test strips	5	5.6	6.4	
Self-treatment[a]	20-40			
Medical consultation	1110	0.25	0.39	
Event total				415.2
Severe hypoglycaemic event not requiring immediate medical assistance				
Test strips	5	5.6	6.4	
Self-treatment[a]	20-40			
Medical consultation	1110	1	1	
Event total				1170
Severe hypoglycaemic event requiring immediate medical assistance				
AED attendance	990	1	1	
In-patient general ward	4680	3	3	
Medical consultation	0	3	3	
Event Total				15,030

AED accident and emergency department

[a] Self-treatment: sugar drinks, snacks, glucose tablets, candy

Table 6 Indirect costs

Variable	Value
Days off work (DOW) CVD	
DoW, MI acute event	8 days
DoW, CHF onset	6 days
DoW, stroke acute event	15 days
DoW, PVD acute event	7 days
Days off work (DOW) renal disease	
DoW, RT acute event	8 days
Days off work (DOW) neurop/pvd/foot ulcer/amp	
DoW, infected ulcer acute event	6 days
DoW, gangrene acute event	22 days
DoW, amputation acute event	38 days
Days off work (DOW) acute events	
DoW, major SHE 2 (during daytime)	3 days
DoW, major SHE 2 (nocturnal)	3 days
DoW, keto acute event	8 days
Mean annual salary—male (HKD)	216,000
Mean annual salary—female (HKD)	168,000

CVD cardiovascular disease, *HKD* Hong Kong Dollar

compared with base case. In scenario 2, the proportion of severe hypoglycaemia requiring medical assistance was adjusted to 50% instead of 11.8% as used in the base case. This enabled examination of the magnitude of impact that medical assistance in severe hypoglycaemic episodes would have on the costs. We also repeated the analysis assuming that the rates of severe hypoglycaemia were the upper bound of 95% confidence interval (CI) of glargine U100 treatment and the lower bound of 95% CI of NPH treatment (scenario 3). However, it should be noted that probabilistic sensitivity analysis in CDM v9.0 excludes variation in the variable (hypoglycaemia rates). The next updated version of CDM will include variation on hypoglycaemia rates. Although the 95% CI was not reported by Pan et al. a poisson distribution was assumed for the number of hypoglycaemic events and in turn a 95% CI was calculated and used. The scenario evaluated the robustness of the results produced by glargine U100 even under extreme unfavorable rates of hypoglycaemic events. Two further scenarios (scenario 4 and 5) were also simulated where an alternative set of risk equations were used, namely the UKPDS and PROcam risk equations. The UKPDS 82 risk equations are used globally in health economic analyses and were therefore applied here. The PROcam risk equation was proven to be a good predictor of cardiovascular outcomes in Asia despite of being developed for Germany, Austria, and Switzerland [43]. The primary outcome of all analyses was the ICER of insulin glargine U100 as compared with NPH insulin. The ICER is the difference in costs between both interventions divided by the difference in the QALYs between the two treatments. As mentioned earlier, a cost-effectiveness threshold of HKD 343,312 was considered appropriate in Hong Kong. Based on WHO recommendation, treatment with glargine U100 would be considered as highly cost-effective if the ICER was below the cost-effectiveness threshold, cost-effective if the ICER did not exceed three times the defined threshold, and not cost-effective if the ICER was more than three times the cost-effectiveness threshold. Treatment with glargine U100 would be classified as dominant or cost-saving compared with NPH if it resulted in concurrent reduction in costs and increase in QALYs.

Table 7 Scenarios summary

Scenario	Description
Scenario 1: LEAD study baseline cohort	Base case analysis repeated using baseline characteristics reported in the LEAD study
Scenario 2: split between SHE1:SHE2 as 1:1	Adjusted the proportion of hypoglycemia requiring (SHE2) versus not-requiring medical (SHE1) assistance to 1:1. In base case, the percentage of SHE2 is set as 11.8% of total hypoglycemia rate
Scenario 3: efficacy adjusted	Assumed that the rates of severe hypoglycaemia were at the upper bound of the 95% CI of glargine U100 treatment and the lower bound of 95% CI of NPH treatment
Scenario 4: PROcam risk equations	Repeated analysis using PROcam risk equations to predict outcomes
Scenario 5: UKPDS 82 risk equations	Repeated analysis using UKPDS 82 risk equations to predict outcomes

SHE1 severe hypoglycemia not requiring medical assistance, *SHE2* severe hypoglycemia requiring medical assistance

Probabilistic sensitivity analysis

In version 9.0 of the CDM, the cohort baseline values (age, duration of diabetes and baseline physiological parameter levels), the treatment effects on physiological parameter levels and transition probabilities for cardiovascular events were subject to random sampling based on their standard error (SE). Direct- and indirect costs are also included in the PSA based on a defined variation of 20%. Utilities and disutilities were reported without SE and as such not considered in the PSA. Finally, please note that version 9.0 of the model does not allow inclusion of hypoglycaemia rates in the PSA. Results of the PSA are the ICER cloud scatterplot and the complementary cost-effectiveness acceptability curve (CEAC).

Results

Base case results: insulin glargine U100 versus NPH insulin

In the base case analysis, 1000 patients were treated with insulin glargine U100 or NPH insulin for a time horizon of 50 years (lifetime) and incurring costs in the public setting. Total costs of treating diabetes which included costs of insulin, costs related to diabetes complications and indirect costs amounted to HKD 762,136 for a patient receiving glargine U100 and HKD 740,776 for a patient using NPH (Table 8). The breakdown of direct costs can be reviewed under Additional file 1: Table S1. The cost breakdown shows total average costs per patient, specifically for treatment, management, and for disease complications over the whole simulation period. Although the upfront cost of glargine U100 treatment was higher than its counterpart NPH, this was partly compensated due to lower costs for hypoglycaemia. Patients treated with glargine U100 suffered significantly fewer hypoglycaemic episodes (Additional file 1: Table S2), hence incurring lower costs (HKD 39,338) than patients treated with NPH (HKD 57,962) (Additional file 1: Table S1). The incremental gains in life expectancy and QALYs for glargine U100 versus NPH were 0.01 years and 0.217 years respectively leading to an ICER of 98,663 HKD per QALY gained (Table 8). The physiological progression of HbA1c of the two treatments can be also observed under Fig. 1 where glargine U100 provided greater reduction in HbA1c levels at the beginning of the treatment which progressed naturally to converge with HbA1c levels of NPH (Fig. 1) (%). A PSA was completed to test the robustness of the results and the ICER scatter plot and accompanying CEAC are shown in Fig. 2a, b. The results for the PSA resulted in a cloud with the major portion existing within the northeast and southeast quadrants. Based on these findings and considering the current willingness-to-pay (WTP) threshold in Hong Kong being HKD 343,312, the probability of glargine U100 being a cost-effective treatment at the defined threshold compared to NPH resided at approximately 75%.

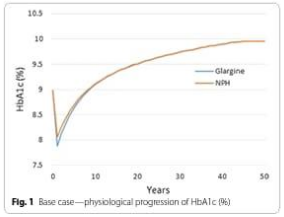

Fig. 1 Base case—physiological progression of HbA1c (%)

Scenarios

Under scenario 1, the analysis was repeated using the baseline characteristics reported in the LEAD study. This resulted in slightly larger incremental gains in favor of glargine U100 compared to the base case (QALY: 0.224 vs 0.217 years) (Table 9). The ICER for this scenario was HKD 107,791 per QALY gained. The result of the PSA is similar to the base case with the probability of being cost-effective at the defined threshold is slightly below 80% (Additional file 2: Figure S1A and B).

In scenario 2, the proportion of severe hypoglycaemia that required medical assistance was equal to that not requiring medical assistance (i.e. 50% versus 50%). The realized ICER under this scenario was HKD 10,583 per QALY gained which was significantly lower in comparison to the base case and all the other scenarios (Table 9). This drop in ICER can be explained by the high cost of severe hypoglycaemia necessitating medical assistance and the lower risk of severe hypoglycaemia associated with glargine U100 compared with NPH. The PSA scatter plot and the constructed CEAC shows that glargine U100 would be cost-saving in approximately 45% of the cases and has 85% probability of being cost-effective at

Table 8 Base case analysis results

	Glargine		NPH		Incremental	
	Mean (SD)	CI (low–high)	Mean (SD)	CI (low–high)	Mean	CI (low–high)
LE (years)	13.522 (0.165)	13.512–13.532	13.512 (0.16)	13.502–13.522	0.01	−0.004 to 0.024
Undiscounted LE (years)	18.763 (0.28)	18.745–18.78	18.746 (0.271)	18.729–18.763	0.017	–
QALY	7.842 (0.105)	7.835–7.848	7.625 (0.104)	7.619–7.632	0.217	0.207–0.226
Undiscounted QALY (years)	10.651 (0.17)	10.641–10.662	10.347 (0.166)	10.337–10.357	0.304	–
Direct costs	701,015 (40,687)	698,493–703,536	678,641 (40,745)	676,115–681,166	22,373	18,726–26,021
Indirect costs	61,121 (6847)	60,697–61,546	62,135 (6637)	61,723–62,546	−1013	−1013 to −1609
Combined costs	762,136 (47,535)	759,190–765,083	740,776 (47,382)	737,839–743,713	21,360	21,360–17,747
ICER					98,663	78,527–120,646

Values are expressed as mean (standard deviation)

HKD Hong Kong Dollar, *ICER* incremental cost-effectiveness ratio, *LE* life expectancy, *LYG* life year gained, *QALY* quality-adjusted life year

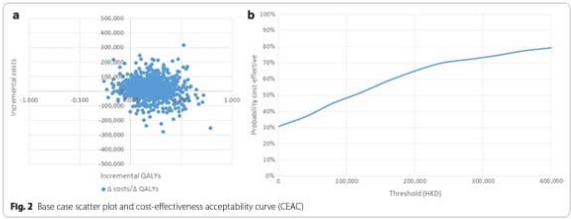

Fig. 2 Base case scatter plot and cost-effectiveness acceptability curve (CEAC)

Table 9 Scenario analyses results

	Glargine		NPH		Incremental	
	Mean (SD)	CI (low–high)	Mean (SD)	CI (low–high)	Mean	CI (low–high)
Scenario 1: LEAD study baseline cohort						
QALY	7.822 (0.108)	7.816–7.829	7.599 (0.11)	7.592–7.606	0.224	0.214–0.233
Combined costs	774,826 (45,795)	771,988–777,664	750,724 (48,371)	747,726–753,722	24,102	20,692–27,511
ICER					107,791	88,809–128,559
Scenario 2: split between SHE1:SHE2 as 1:1						
QALY	7.83 (0.101)	7.823–7.836	7.561 (0.103)	7.554–7.567	0.269	0.26–0.278
Combined costs	766,965 (46,814)	764,063–769,866	764,116 (46,878)	761,210–767,021	2848	−644 to 6341
ICER					10,583	−2317 to 24,391
Scenario 3: efficacy adjusted for both treatment arms						
QALY	7.81 (0.107)	7.803–7.816	7.673 (0.104)	7.667–7.68	0.137	0.127–0.146
Combined costs	772,351 (48,678)	769,334–775,368	737,801 (50,299)	734,683–740,918	34,550	30,814–38,285
ICER					253,115	211,061–301,461
Scenario 4: using PROcam risk equations						
QALY	7.06 (0.101)	7.054–7.066	6.87 (0.095)	6.864–6.876	0.19	0.181–0.199
Combined costs	674,151 (42,343)	671,527–676,776	658,559 (41,865)	655,964–661,153	15,592	12,621–18,563
ICER					82,023	63,427–102,560
Scenario 5: using UKPDS 82 risk equations						
QALY	7.837 (0.12)	7.829–7.844	7.63 (0.113)	7.623–7.637	0.206	0.196–0.217
Combined costs	686,804 (48,701)	683,785–689,823	670,520 (48,519)	667,512–673,527	16,284	12,703–19,865
ICER					78,897	58,540–101,355

Values are expressed as mean (standard deviation)

ICER incremental cost-effectiveness ratio, *QALY* quality-adjusted life-year, *SHE1* severe hypoglycaemic event (not requiring medical assistance), *SHE2* severe hypoglycaemic event (requiring medical assistance)

the willingness-to-pay threshold in Hong Kong of HKD 343,312 (Additional file 2: Figure S1C and D).

The analysis for scenario 3 assumed that the rates of severe hypoglycaemia were at the upper bound of the 95% CI of glargine U100 treatment and the lower bound of 95% CI of NPH treatment which effectively attenuated the difference in the rates of hypoglycaemia between the two treatments. The ICER under this scenario at HKD 253,115 was higher than that of the base case (Table 9). Furthermore, the PSA shows a slight shift of the bootstrap cloud towards the left northwest quadrant (Additional file 2: Figure S1E and F) implying cases where insulin Glargine U100 results in less QALYs compared to NPH insulin. This effect is minimal however, and glargine U100 was still considered cost-saving in approximately 25% of the cases and is expected to be 55% cost-effective at the Hong Kong WTP threshold.

In scenario 4, the same base case settings were repeated but using the PROcam risk equations. The analysis produced an estimated ICER of HKD 82,023 per QALY gained (Table 9). The results of the PSA seen under the ICER scatter plot and the CEAC resemble closely the results shown under the base case where glargine U100 would be considered a cost-effective treatment in almost 75% of the simulations versus NPH (Additional file 2: Figure S1G and H). Scenario 5 again utilized a different set of risk equations, specifically the UKPDS 82 risk equations. The incremental cost effectiveness ratio was calculated to be HKD 78,897 per QALY gained for glargine U100 compared with NPH, thus lower than the base case (Table 9). The ICER scatter plot and the CEAC are shown in Additional file 2: Figure S11 and J.

Discussion

The current analysis showed that insulin glargine U100 is highly cost-effective in comparison to NPH insulin from a societal perspective in Hong Kong, both under base case and scenario analyses. The calculated ICER of HKD 98,663 per QALY gained (base case) is deemed highly cost-effective and is mainly driven by the reduced rates of hypoglycaemic events experienced with glargine U100. The results from the PSA further supported the robustness of the calculated ICER and glargine U100 is expected to be cost-effective in real-life if it would be reimbursed in Hong Kong.

The analysis was based on clinical data extracted from the LEAD study which is the only published trial to date that compares insulin glargine U100 with NPH insulin in Asia including Hong Kong. In turn, the current cost-effectiveness analysis is the first to utilize Asian-specific clinical data to compare glargine U100 and NPH using the validated Core Diabetes Model. All the scenarios that were defined and run consistently showed that glargine U100 is cost-effective with ICERs well below the local WTP threshold.

From a clinical perspective, insulin glargine U100 has been demonstrated to produce greater reduction in HbA1c levels than NPH insulin [7]. Importantly, patients treated with glargine U100 experienced fewer events of hypoglycaemia compared with those treated with NPH. The higher upfront drug acquisition costs for glargine U100 compared to NPH were partly offset by the significantly lower rates of hypoglycaemia and consequentially the costs incurred to manage these events. The base case ICER falls approximately below one-third the defined WTP threshold in Hong Kong making glargine U100 a highly cost-effective insulin option in patients with type 2 diabetes. Even in the worst scenario where the number of hypoglycaemia with NPH was put at the lower bound, and that with glargine U100 at the upper bound, glargine U100 remained cost-effective with an ICER below the defined reimbursement threshold (scenario 3).

It is worth noting that the additional glucose lowering effect of glargine U100 compared with NPH did not lead to a significant reduction in the rates of vascular complications from diabetes or improvement in life expectancy in the present analysis. This is not unexpected since the between-group difference in attained HbA1c was too small to have a sustained impact. As seen in other trials, long-term vascular and mortality benefits from intensive glycaemic control were observed only in younger patients with shorter disease duration and not in older adults with long-standing diabetes and multiple co-morbidities [44, 45]. The ORIGIN trial which randomized over 12,000 individuals with type 2 diabetes or pre-diabetes to glargine U100 or placebo showed that glargine U100 did not reduce incident cardiovascular events [46]. Thus, the cost benefits of insulin glargine U100 were primarily driven by lower rates of hypoglycaemia rather than down-stream effects on vascular complications and life-expectancy.

The results from this cost-effectiveness analysis concur with previous analyses comparing insulin glargine U100 with NPH insulin. Brandle et al. [9] used the IQVIA™ Core Diabetes Model (CDM) on the Swiss population and concluded that in the worst case scenario where baseline HbA1c was 8.0% and absolute HbA1c reduction of 0.96% and 0.84% were achieved with the respective use of glargine U100 and NPH, the ICER with glargine U100 was 49,468 Swiss Franc (CHF) per QALY, which was below the WTP threshold of CHF 65,000 (USD 50,000). In the best-case scenario assuming a greater reduction in HbA1c of 1.24%, glargine U100 was in fact cost-saving. In another study by Grima et al. [10], a state transition model based on data from the UKPDS was applied with Canadian costing, and glargine U100 compared to NPH yielded an ICER of 8618 Canadian Dollars ($CAN) per QALY gained.

Limitations

The study has a number of limitations that need to be acknowledged. Firstly, the efficacy rates of insulin glargine U100 compared with NPH insulin were based on the results of a single clinical trial. For reasons related but not limited to patient selection, treatment compliance, and overall medical care delivered, results from clinical trials are often not reproducible in real world clinical practice. For instance, it is possible that the frequency of severe hypoglycaemia in our local setting differ from that reported in the LEAD trial which could affect the outcome of the analysis. On the other hand, the LEAD study was conducted in Asia with inclusion of patients from Hong Kong. In this regard, clinical profile and responses to treatment should approximate that of patients in Hong Kong. Secondly, some of the baseline characteristics and management settings were not available in the LEAD study or the HKDR and were filled in with default values of the CDM which might not be specific to the local disease population. However, such a limitation is considered common among cost-effectiveness studies and is expected to have only minimal effect on the results. Thirdly, the unit costs of some medical procedures that were considered complex were based on inputs from medical experts in Hong Kong and could vary slightly compared to the realistic procedures used. Again, it is believed that these slight variations would not affect the overall results of the analyses since the medical resources used were based on the rates of the occurrence of adverse events which in turn were based on published literature. Fourthly, we assumed that the dose of insulin was fixed after the second year. In actual practice, insulin regimen would be adjusted, for instance, an increase of basal insulin dose, a change to pre-mixed insulin, or addition of prandial insulin. Although the exact impact of this manoeuvre cannot be determined, it is reasonable to deduce that insulin adjustment pertains to both glargine U100 and NPH groups equally and should not greatly alter the conclusion of the study. Lastly, the Asian population is different from the Western population with respect to risks of complications characterised by more strokes and fewer myocardial infarctions among Asians. We corrected for this by applying Hong Kong-specific risk equations, although testing with the UKPDS 82 equation did not alter the results strongly.

Conclusion

Insulin glargine U100 is a cost-effective treatment for patients with type 2 diabetes when compared with NPH insulin in the Asian setting in Hong Kong. The major driver was the significantly lower rates of hypoglycaemia of glargine U100 than NPH. All the scenarios conducted under the current analysis proved glargine U100 being cost-effective even when the rates of hypoglycaemia were increased for glargine U100 and lowered for NPH. To conclude, these results support the use of insulin glargine U100 in Hong Kong even when the upfront drug acquisition costs are deemed higher than NPH insulin.

Additional files

Additional file 1: Table S1. Base Case Breakdown of direct costs.
Table S2. Results of hypoglycaemia adverse events (per patient).

Additional file 2: Figure S1. Scatterplots and CEACs of the different scenarios.

Abbreviations

AED: accident and emergency department; BMI: body mass index; CDM: Core Diabetes Model; CEAC: cost effectiveness acceptability curve; CHF: Swiss Franc; GDP: gross domestic product; GFR: glomerular filtration rate; GRP: gastrin-releasing peptide; HA: Hospital Authority; HbA1c: glycated haemoglobin; HDL: high density-lipoprotein; HKD: Hong Kong Dollar; HKDR: Hong Kong Diabetes Registry; ICER: incremental cost-effectiveness ratio; LDL: low density-lipoprotein; LEAD: Lantus evaluation in Asian diabetics; LVH: left ventricular hypertrophy; LYG: life year gained; ME: macular oedema; NPH: neutral protamine Hagedorn; NSHE: non-severe hypoglycaemic event; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year; QALY: quality adjusted life-year; SHE 1: severe hypoglycaemic event (not requiring medical assistance); SHE 2: severe hypoglycaemic event (requiring medical assistance); SVL: severe vision loss; T2DM: type-2 diabetes mellitus; uACR: urine albumin-to-creatinine ratio; UKPDS: United Kingdom Prospective Diabetes Study; USD: United States Dollar; WHO: World Health Organization; WTP: willingness-to-pay.

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Authors' contributions

EL and AL collected, analysed, and interpreted the data for the current analyses; in addition to also writing the manuscript. ICNC, WYS, and AK have provided substantial contributions in the conceptual design of the study, in addition to critically revising the manuscript for clinical and intellectual content. AS and ML assisted in populating the model, run the analyses, and conduct the quality assurance. They contributed to the manuscript writing. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analysed during this study are included in this published article and its Additional files.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

AL received a research grant from Sanofi Limited for conducting this study. Sanofi had no role in study design, data collection, analysis, or interpretation of the data.

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