Jurnal Manajemen dan Pelayanan Farmasi (JMPF)
(Journal of Management and Pharmacy Practice)
ISSN-p : 2088-8139 | ISSN-e : 2443-2946
JMPF Vol 14(4) 2024: 291-298

Cost-effectiveness Study in Type 2 Diabetes Mellitus in Asia: A Review

I Made Wiracana[1], Nunung Priyatni[2], Dita Maria Virginia[2]*

1. Student of Master Degree Program, Universitas Sanata Dharma, Yogyakarta, Indonesia
2. Department of Pharmacy, Universitas Sanata Dharma, Yogyakarta, Indonesia

ARTICLE INFO
Submitted : 02-01-2024
Revised : 27-02-2024
Accepted : 03-09-2024

Published : 31-12-2024

Corresponding Author:
Dita Maria Virginia

Corresponding Author Email:
virginia@usd.ac.id

ABSTRACT

Background: Type 2 Diabetes Mellitus (DM) requires intensive treatment to prevent progression and complications. One of the intensive treatments is insulin therapy. The increase in insulin price and variation in insulin therapy results in differences in treatment costs. In Asia, commonly used types of insulin therapy are NPH insulin and glargine insulin. It is urgent to define the most cost-effective insulin therapy among type 2 DM patients because of the economic burden.

Objectives: This study aims to assess the cost-effectiveness of these insulin types. We did a narrative review using literature discussing the cost-effectiveness of insulin for type 2 DM patients.

Methods: This study employs a narrative review approach using the PRISMA-P 2015 structured approach to examine studies. This article's methodological quality was evaluated using the Drummond checklist. The terms "cost-effectiveness analysis," "diabetes mellitus type 2," and "insulin" were used in the literature search for this study.

Results: We obtained five pieces of literature fulfilling inclusion and exclusion criteria. The results indicated that the age range of type 2 DM patients in this study is 57-62 years, with a majority being women. The most frequently occurring complication is cardiovascular complications. NPH insulin and glargine insulin were the most extensively studied insulins in the literature review.

Conclusion: Based on the cost-effectiveness analysis, glargine insulin is more cost-effective than NPH insulin in Asia due to the rare occurrence of hypoglycemia which is a common side effect as a treatment outcomes.

Keywords: Asia; cost-effectiveness; DM type 2; Insulin NPH; Insulin glargine

INTRODUCTION

Diabetes Mellitus (DM) is a common term for a group of metabolic disorders characterized by hyperglycemia resulting from impaired insulin secretion, insulin effectiveness, or both.[1] Chronic hyperglycemia associated with diabetes is linked to long-term organ damage, dysfunction, and failure, particularly in the eyes, kidneys, nerves, heart, and blood vessels. Among diagnosed cases of DM, 5.8% are classified as type 1 diabetes, while 90.9% are classified as type 2 diabetes.[2]

According to the latest data from the International Diabetes Federation (IDF), the global prevalence of type 2 diabetes mellitus in adults is 536.6 million people (10.5%) in 2021.[3] In 2019, 10.7 million people in Indonesia had diabetes, making it one of the countries with the highest absolute prevalences globally. Approximately 812.204 people were identified with a diagnosis of type 2 diabetes mellitus based on National Health Insurance (JKN) data.[4]

Type 2 DM requires intensive therapeutic management to prevent disease progression and complications. The principles of managing type 2 DM include non-pharmacological interventions such as adopting a healthy lifestyle and pharmacological interventions such as oral antidiabetic (OAD) therapy, either alone or in

combination with insulin.[5] Insulin is an essential medication in the management of type 1 DM and is also used in certain cases of type 2 diabetes.[6]

The variation in insulin therapy utilization results in differences in treatment costs.[7] Specifically in India, the latest expensive insulin promoted and frequently prescribed costs INR 1800 (30 USD) per vial, making insulin degludec more expensive in India compared to Europe, and 50% more expensive than human insulin compared to NPH, sold at INR 133 (2.2 USD). Additionally, the average price list of insulin has nearly tripled from 2002 to 2013. Between 2001 and 2015, lispro and human insulin became expensive by 585% (from 35 to 234 USD per vial) and 555% (from 20 to 131 USD per vial), respectively.[8] The economic burden associated with DM treatment necessitates a cost-effectiveness analysis to aid decision-making in selecting more cost-effective treatment options.[9]

Pharmacoeconomics is the foundation of Health Technology Assessment (HTA), but its uptake in Asia has historically been sluggish. The lack of awareness and the lack of country-specific epidemiological, clinical, and health economics data, together with fragmented research efforts, are some of the factors that have contributed to the sluggish adoption of HTA across Asia.[10] Pharmacoeconomic studies will help determine treatment choices for DM by considering the cost-effectiveness of the therapies provided.[11] Cost-effectiveness analysis aids in determining the value of money or efficiency, which enables decision-makers to deploy resources effectively.[12] The study aims to investigate the cost-effectiveness of insulin utilization among type 2 diabetes patients.

METHODS

Inclusion and Exclusion Criteria

The literature utilized in this study must meet the following criteria: (1) written in both English and Indonesian languages, (2) published between 2013 to 2023, (3) accessible through electronic databases such as PubMed and Google Scholar, (4) focus on the cost analysis of treatment for patients diagnosed with Type 2 Diabetes Mellitus who use insulin, (5) provide patient profile information, including gender, age, blood glucose levels, Body Mass Index (BMI), complications or comorbidities, and conducted in Asian regions. Exclusion criteria include studies involving therapies other than insulin, lack of initial patient profile description (baseline), and articles that do not discuss the influence of costs on patient treatment.

Method

This study employs a narrative review approach using the PRISMA-P 2015 structured approach to examine studies. The methodological quality of this article was appraised using Drummond checklist.[13]

Literature Search Strategy

Literature search in this study utilized the keywords "cost-effectiveness analysis," "diabetes mellitus type 2," and "insulin." The literature publications were restricted to the period from 2013 to 2023. Subsequently, the literature search was conducted based on title, author names, contextual references, and library variables.

Data Extraction

Data extraction was performed by reviewing the population, intervention, outcome, and results, which were then recorded in a table based on an extraction form containing the following information: (1) author(s), (2) year of publication, (3) population criteria, (4) intervention, (5) comparator, (6) outcome.

Data Synthesis

Data synthesis was conducted by analyzing the effectiveness of single or combination insulin therapy in patients with type 2 diabetes mellitus using a narrative approach. The obtained literature was subjected to critical appraisal by two researchers and discussed until conclusions were reached.

RESULTS AND DISCUSSION

Data from the literature studies indicate that the age range of patients with type 2 diabetes mellitus receiving insulin therapy varies from 57 years to 62 years. According to the CDC, the majority of type 2 diabetes patients fall within the age range of 45-64 years, where there is an increased insulin resistance and pancreatic cell dysfunction among individuals above 45 years of age. In this literature study, the majority of individuals with type 2 diabetes were women.[14] The higher prevalence of type 2 diabetes among women is associated with lower physical activity levels and a higher prevalence of obesity among women.[5] The HbA1c levels in the literature

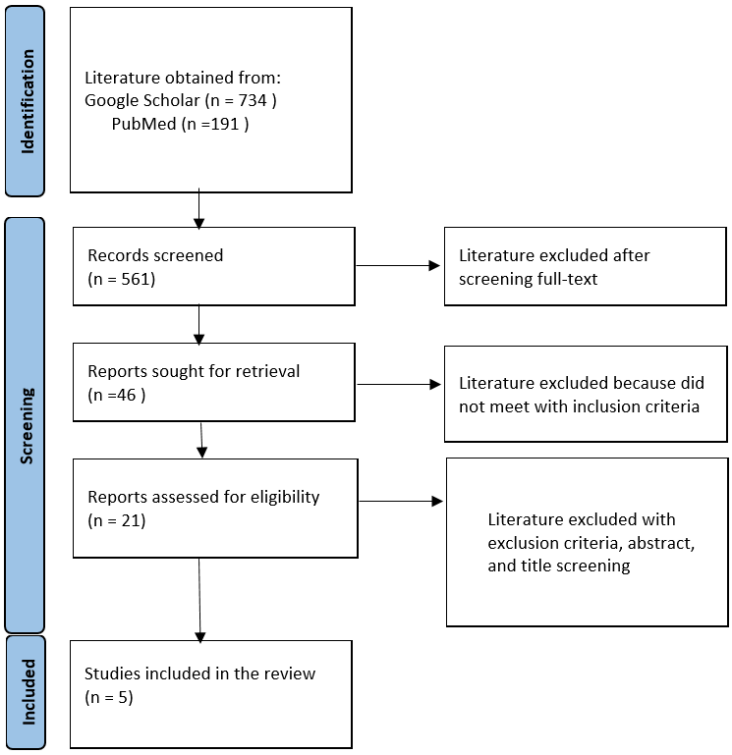

Figure 1. Diagram of articles included in the analysis

studies ranged from 8.1% to 9.55%. According to the recommended insulin therapy guidelines in Indonesia, basal insulin can be initiated in combination with dual/triple oral antidiabetic drugs (OAD) if the HbA1c levels range from 7.5% to 9% and the diabetes has been present for a long duration.[15] Body Mass Index (BMI) values are divided into five categories based on WHO criteria: underweight (<17.0 kg/m2), mild underweight (17.0-18.4 kg/m2), normal weight (18.5-25.0 kg/m2), mild overweight (25.1-27.0 kg/m2), and overweight (≥27.0 kg/m2).[16]

The sample size in this literature study varies from 174 patients to 9,419 patients. The variation in patient sample sizes is attributed to differences in methods and modeling used. The lowest sample size is from the study by Farschi et al (2016) because the research employed a pharmacoeconomic study method simultaneously with clinical trials, while other studies in this literature review used pharmacoeconomic study methods with modeling. Despite several proposed methods as a basis for calculating sample size for pharmacoeconomic studies conducted alongside clinical trials, a standardized formula that can be practically and universally accepted is not yet available.[17] On the other hand, studies utilizing modeling methods yield larger sample sizes, as exemplified by the research conducted by Permsuwan et al (2017) with 9,419 patients. This increase is attributed to the utilization of the Thai Database Registry (TDR) database, allowing for simulation modeling.[18] Based on this literature study, most individuals with type 2 diabetes were classified as mildly overweight or overweight. The risk of developing type 2 diabetes increases proportionally with the incidence of diabetes, with a 23% increased risk for every unit increase in BMI (kg/m2).[19]

The most commonly occurring complications from the literature studies are cardiovascular complications (myocardial infarction, angina pectoris, stroke, peripheral vascular disease, congestive heart failure), microalbuminuria, and neuropathy. Type 2 diabetes mellitus is often associated with an increased risk of cardiovascular complications. One mechanism linking type 2 diabetes to cardiovascular complications is the occurrence of low-grade inflammation. Type 2 diabetes and insulin resistance are associated with excessive expression of several cytokines by adipose tissue, including tumor necrosis factor-alpha, interleukin-1, interleukin-6, leptin, resistin, monocyte chemoattractant protein-1, plasminogen activator inhibitor-1, fibrinogen, and angiotensin. The excessive expression of these cytokines contributes to increased inflammation and lipid accumulation, which have detrimental effects on blood vessels and can lead to endothelial dysfunction, myocardial infarction, and cardiomyopathy.[20]

Shaffie and Ng (2020) examined insulin glargine and NPH, as well as insulin detemir and NPH, in a Malaysian study. The study utilized the UKPDS OM 2.0 modeling. This modeling is a computerized simulation tool

Table I. Characteristics of the Literature Reviewed

No	Country, Author	Characteristics of the Patients	Intervention and Comparator	Clinical Outcome, QALY	Cost	ICER
1	Malaysia Shafie and Ng, 2020	Age: Average 62 Hba1C: Average 8.2 Time Horizon: 40 years Sample size: 2000 patients	NPH insulin insulin glargine insulin detemir	improvement in QALY (between +0.1317 (insulin Glargine) and +0.8567 (insulin Detemir)) in patients with LAIA compared with NPH insulin.	insulin glargine: 4,867 MYR per 0.1317 per QALY gained insulin detemir: 6,026 MYR per 0.8567 per QALY gained	insulin detemir is dominant
2	Iran, Farschi et al, 2016	age: 57.24 – 58.5 HbA1c: 9.55-9.75% BMI: 29.57 – 31.78 kg/m2 observation period: 48 weeks Sample size: 174 patients	Biphasic Aspart 30 NPH regular	Biasp 30: HbA1c decrease to 7.15% QALY increase to 0.73 NPH reg: HbA1c decrease to 7.62% QALY increase to 0.66	930.5 ± 81.4 for BiAsp 30, 1101.3 ± 165.5 for NPH reguler	ICER was approximately 20000 $ per QALY. Regarding major clinical outcomes (i.e. hypoglycemia events and QALY) BIAsp 30 showed lower ICER as a dominant alternative
3	Thailand, Permsuwan et al, 2016	Average age: 60.9 years HbA1c 8.1 % BMI 25.7 Sample size: 751 patients	Insulin glargine Neutral Protamin Hagedorn	QALY for Biasp 30 is 8.838, and for NPH is 8.350	US$2,977.90 (glargine) vs. US$228.31 (NPH)	ICER value is 244.915 US/QALY
4	Hongkong, Lau et al, 2019	mean age 57.28 years, mean BMI 25.36 kg/m2, HbA1C 8,98 %, Sample size: 2344 adults	Insulin glargine Insulin NPH	Insulin glargine QALY vs Insulin NPH (7,842 vs 7,625)	insulin glargine cost 762,136 HKD and insulin NPH cost 740,776 HKD	ICER value is 98,663 HKD/QALY
5	Thailand, Permsuwan et al, 2017	mean age 60,9 years, mean BMI 25.7 kg/m2, HbA1C 8.1 % Sample size: 9,419 patients	insulin glargine Insulin detemir	Insulin glargine QALY vs Insulin detemir (8.908 vs 8.921)	Insulin glargine cost 2,405,599 THB and insulin detemir cost 3,262,268 THB	ICER value is 285,556,370 for insuline glargine vs insuline detemir

BMI: body mass index; HKD: Hongkong Dolar; THB: Thailand Bath; HbA1c: Hemoglobin A1c; NPH: Neutral protamine hagedorn; US$: US Dolar; BiAsp: Biphasic Aspart; QALY: Quality Adjusted Life Years

designed to estimate Life Expectancy, Quality Adjusted Life Years, Quality, and cumulative costs of complications in patients with type 2 diabetes mellitus (T2DM). It applied equations and peer-reviewed algorithms published in the UK Prospective Diabetes Study (UKPDS).[21] Insulin detemir and glargine have higher costs compared to NPH insulin but have higher QALY values due to lower complication rates and hypoglycemic events. Although insulin glargine and detemir are more cost-effective compared to NPH, the obtained ICER values are higher than the accepted willingness-to-pay threshold set by the Malaysian government (RM 29,080/QALY).[22]

Insulin BiAsp 30 and insulin NPH were examined in an Iranian study by Farschi et al. (2016). The study was conducted over 48 weeks. The QALY value was obtained using the EQ-5D-3L questionnaire and the Visual Analogue Scale (VAS). The European Quality of Life-5 Dimensions 3 Level version (EQ-5D-3L) was used, which was developed by EuroQol from the UK. This questionnaire consists of 5 dimensions: 1) mobility/walking, 2) self-care, 3) usual activities, 4) pain/discomfort, and 5) anxiety/depression. Each dimension has 3 levels of response: 1) no problems, 2) moderate problems, and 3) severe problems. Each level in the dimension has different coefficients. A value of 100% or 1000 indicates perfect health.[23] The study calculated the costs of each intervention (direct and indirect) as well as the side effects (hypoglycemia and weight gain). The conclusion obtained was that insulin BiAsp 30 is more cost-effective in terms of dominance (higher effectiveness and lower cost) compared to insulin NPH.[24]

A Hong Kong study by Lau et al. (2019) contrasted insulin NPH with insulin glargine. The QVIA™ Core Diabetes Model (CDM) v9.0 was used to assess the costs incurred during treatment and the outcomes achieved. CDM is often used as a policy analysis tool because it is a non-product-specific model. It consists of a set of 15 sub-models, where each sub-model is a combination of a semi-Markov model structure and Monte Carlo simulation, which simulate major diabetes complications including, but not limited to, congestive heart failure, myocardial infarction, stroke, end-stage renal disease, lower extremity amputation, foot ulcers, and hypoglycemia. This model uses time-dependent probabilities, states, and diabetes types derived from published sources. CDM projects outcomes for the population based on the following lists: initial cohort characteristics, history of past complications, concomitant treatments, and changes in physiological variables over time. From these, the model can calculate complication events, life expectancy, quality-adjusted life expectancy, and total costs in the population. The calculated costs include direct and indirect costs. The results obtained indicate that insulin glargine was more cost-effective than insulin NPH with an ICER value of 98.663.[25]

A 2016 study by Permsuwan et al. in Thailand comparing NPH therapy with insulin glargine. The study utilized the IMS CORE Diabetes Model version 8.5 (CDM), a computer simulation model. The research perspective was from the national insurance, so only direct costs of medication, therapy management, diabetes-related complications, and associated side effects were considered. The results showed that insulin glargine therapy was more cost-effective compared to NPH insulin due to the higher QALY value obtained with insulin glargine. The ICER value obtained was 244,915 THB/QALY. However, the ICER value obtained was still above the willingness-to-pay threshold set by the Thai government, which is THB 160,000/QALY.[14]

A study conducted by Permsuwan et al. (2017) in Thailand compared insulin glargine vs detemir therapy. The study utilized the IMS CORE Diabetes Model version 8.5 (CDM), a computer simulation model. The IMS CORE Diabetes Model (CDM) is a simulation model that predicts long-term health outcomes and costs associated with the management of T1DM and T2DM. The CDM has been extensively used to evaluate the cost-effectiveness of new therapy options for diabetes treatment. The model is also routinely used to inform reimbursement decisions, public health issues, resource planning, clinical trial designs, and optimal patient management strategies.[26] The results showed that insulin detemir had higher total costs compared to insulin glargine. However, when measuring insulin detemir as a single dose, it was dominant (lower cost and higher effectiveness) compared to insulin glargine. The ICER value obtained was 856,899.[18]

Based on Table II, the costs incurred for each therapy in various countries in Asia are described. There are differences in costs even for the same type of therapy. This is due to the different perspectives used in each pharmacoeconomic study. Malaysia and Thailand adopt a payer perspective, Iran uses a patient perspective, and Hong Kong applies a social perspective. The difference in perspectives significantly influences the total costs incurred in a therapy. From the payer perspective, it usually includes only medical costs. This perspective is commonly used by state-owned insurance providers. The patient perspective includes medical costs, direct non-medical costs (such as transportation expenses), and productivity loss costs. On the other hand, the social perspective encompasses medical costs, direct non-medical costs (such as transportation and informal expenses), and productivity loss costs.[27] Insulin NPH and insulin glargine are the most extensively researched insulins in this literature study. Insulin NPH is widely studied due to its more economical price compared to analog insulins.[28] On the other hand, insulin glargine is frequently prescribed and considered the gold standard in basal

Table II. The Costs Associated with Each Literature

	Malaysia	Iran	Hongkong	Thailand (1)	Thailand (2)
NPH	33,182 RM (7,503.84 USD)	1,101.24 USD	740,776 HKD (94,367.87 USD)	541,806 THB (15,790.11 USD)	
Glargine	38,151 RM (8,627.54 USD)		762,136 HKD (97,088.93 USD)	661,344 THB (19,273.86 USD)	2,405,599 THB (70,107.51 USD)
Detemir	39,209 RM (8,866.80 USD)				3,262,268 THB (95,073.82 USD)
BiAsp 30		930.55 USD			

NPH: Neutral Protamine Hagedorn, BiAsp: Biphasic Aspart, RM: Ringgit Malaysia, HKD: Hongkong Dolar, THB: Thailand Bath, USD: US Dolar; Perspective: Malaysia: Payer, Iran: Patient, Hongkong: Social, Thailand: Payer

insulin therapy. Additionally, insulin glargine can be safely and effectively used in various stages of injection therapy, ranging from initial basal insulin therapy combined with oral antidiabetic medicines to different combination therapies.[29]

Compared to NPH insulin, basal insulin analogs have demonstrated several benefits, such as reduced pharmacological fluctuations, a decreased likelihood of hypoglycemia, and a more significant influence on overall quality of life. The clinically significant reduction in the risk of hypoglycemia by insulin glargine compared to NPH in patients with T2DM is expected to be a major contributor to the cost-effectiveness of insulin glargine, as significant savings can be achieved with lower hypoglycemia treatment costs.[30,31] Regarding cardiovascular complications, insulin glargine reduces triglyceride levels, causes a low increase in body weight, decreases hypoglycemia compared to NPH, and has a neutral effect on blood pressure. The ORIGIN trial, a specific cardiovascular outcome trial of glargine, did not show an increased risk of cardiovascular events.[32] According to the study by Wolnik et al. (2020), insulin glargine achieved a reduction in HbA1c of ≥0.5% from baseline to 6 months after switching from NPH insulin in 71.7% of participants. At 3 and 6 months, there was a significant average reduction in HbA1c of 0.77% and 1.01%, respectively.[33] In addition, insulin glargine is also effective with a good safety profile in both younger and older patients with uncontrolled T2DM, indicating that insulin glargine can be a suitable treatment option for elderly patients representing a vulnerable population susceptible to hypoglycemia.[34]

CONCLUSION

Insulin NPH and insulin glargine have been extensively studied in the literature due to the cost-effectiveness of NPH insulin, which is cheaper than analog insulins, and the widespread prescription of insulin glargine for basal insulin therapy in Asia. In the studies included in the literature, insulin glargine is found to be more cost-effective than NPH insulin in Asia because it has a lower occurrence of side effects, particularly hypoglycemia, which is a common concern in diabetes treatment.

ACKNOWLEDGEMENT

IMW and NP together did literature searching and compiled the script. DMW supervised the project. All authors contributed to the final version of the manuscript. None to declare for funding.

CONFLICT OF INTEREST

None to declare

REFERENCES

1. Petersmann A, Nauck M, Müller-Wieland D, et al. Definition, classification and diagnostics of diabetes mellitus. *J Lab Med*. 2018;42(3):73-79. doi:10.1515/labmed-2018-0016
2. Bullard KM, Cowie CC, Lessem SE, et al. Morbidity and Mortality Weekly Report Prevalence of Diagnosed Diabetes in Adults by Diabetes Type-United States, 2016. *Morb Mortal Wkly Rep*. 2016;67(12):2016-2018. doi:10.1097/EDE.0b013e31829ef01a
3. Yan Y, Wu T, Zhang M, Li C, Liu Q, Li F. Prevalence, awareness and control of type 2 diabetes mellitus and risk factors in Chinese elderly population. *BMC Public Health*. 2022;22(1):1-6. doi:10.1186/s12889-022-13759-9

4. Hidayat B, Ramadani RV, Rudijanto A, Soewondo P, Suastika K, Siu Ng JY. Direct Medical Cost of Type 2 Diabetes Mellitus and Its Associated Complications in Indonesia. *Value Heal Reg Issues*. 2022;28:82-89. doi:10.1016/j.vhri.2021.04.006
5. Suprapti B, Widyasari N, Rahmadi M, Wibisono C. Review of insulin therapy in type 2 diabetes mellitus ambulatory patients. *Indones J Pharm*. 2017;28(4):221-231. doi:10.14499/indonesianjpharm28iss4pp221
6. Phulpagare MB, Tiwari SA, Hiray RS. Cost Excursion Study of Various Insulin Preparations Available in India. *J Clin Diagnostic Res*. Published online 2021:3-7. doi:10.7860/jcdr/2021/48116.15107
7. Anggriani Y, Rianti A, Pratiwi AN, Khairani S. Evaluasi Biaya Pengobatan Pada Pasien Diabetes Melitus Tipe 2 Rawat Jalan dengan Terapi Insulin di RSUP X di Jakarta Periode Januari 2016-Desember 2017 Treatment Cost Evaluation of Type 2 Diabetes Mellitus Outpatient Patients Receiving Insulin Therapy at. *Pharm J Indones*. 2018;4(2):91-97.
8. Zargar AH, Kalra S, K M PK, et al. Rising cost of insulin: A deterrent to compliance in patients with diabetes mellitus. *Diabetes Metab Syndr Clin Res Rev*. 2022;16(8):102528. doi:10.1016/j.dsx.2022.102528
9. Fitriyani F, Andrajati R, Trisna Y. Analisis Efektivitas-Biaya Terapi Kombinasi Metformin-Insulin dan Metformin-Sulfonilurea pada Pasien Rawat Jalan dengan Diabetes Melitus Tipe 2 di RSUPN Dr. Cipto Mangunkusumo. *Indones J Clin Pharm*. 2021;10(1):10. doi:10.15416/ijcp.2021.10.1.10
10. Liu G, Wu EQ, Ahn J, Kamae I, Xie J, Yang H. The Development of Health Technology Assessment in Asia: Current Status and Future Trends. *Value Heal Reg Issues*. 2020;21:39-44. doi:10.1016/j.vhri.2019.08.472
11. Laelasari E, Sauriasari R, Banun A. Cost-effectiveness analysis of insulin, sulfonylurea, and sulfonylurea–Metformin in type 2 diabetes mellitus. *Asian J Pharm Clin Res*. 2017;10(Special Issue October):50-53. doi:10.22159/ajpcr.2017.v10s5.23094
12. Thomas D, Hiligsmann M, John D, Al Ahdab OG, Li H. *Pharmacoeconomic Analyses and Modeling*. Elsevier Inc.; 2018. doi:10.1016/B978-0-12-814276-9.00018-0
13. Drummond M., Jefferson T.O. Guideline for Authors and Peer Reviewers of Economic Submissions to the BMJ. *BMJ*. 1996;313(2):275-283.
14. Permsuwan U, Chaiyakunapruk N, Dilokthornsakul P, Thavorn K, Saokaew S. Long-Term Cost-Effectiveness of Insulin Glargine Versus Neutral Protamine Hagedorn Insulin for Type 2 Diabetes in Thailand. *Appl Health Econ Health Policy*. 2016;14(3):281-292. doi:10.1007/s40258-016-0228-3
15. Chan SP, Aamir AH, Bee YM, et al. Practical Guidance on Basal Insulin Initiation and Titration in Asia: A Delphi-Based Consensus. *Diabetes Ther*. 2022;13(8):1511-1529. doi:10.1007/s13300-022-01286-0
16. Nugroho PS, Wijayanti AC. Indeks Masa Tubuh Dan Kaitannya Dengan Diabetes Melitus Pada Umur > 15 Tahun Di Indonesia, Studi Data Survei Kehidupan Keluarga Indonesia V. *J Publ Kesehat Masy Indones*. 2018;5(1):12. doi:10.20527/jpkmi.v5i1.4998
17. Setiawan D, Endarti D, Suwantika A. *Farmakoekonomi Modeling*. UM Purwokerto Press; 2017.
18. Permsuwan U, Thavorn K, Dilokthornsakul P, Saokaew S, Chaiyakunapruk N. Cost-effectiveness of insulin detemir versus insulin glargine for Thai type 2 diabetes from a payer's perspective. *J Med Econ*. 2017;20(9):991-999. doi:10.1080/13696998.2017.1347792
19. Chen Y, Zhang XP, Yuan J, et al. Association of body mass index and age with incident diabetes in Chinese adults: A population-based cohort study. *BMJ Open*. 2018;8(9):1-9. doi:10.1136/bmjopen-2018-021768
20. Leon BM. Diabetes and cardiovascular disease: Epidemiology, biological mechanisms, treatment recommendations and future research. *World J Diabetes*. 2015;6(13):1246. doi:10.4239/wjd.v6.i13.1246
21. University of Oxford, Diabetes Trials Unit, Health Economics Research Centre. UKPDS Outcomes Model User Manual. 2015;(May):1-10. http://www.dtu.ox.ac.uk/outcomesmodel/UKPDSOutcomesManual.pdf
22. Shafie AA, Ng CH. Cost-effectiveness of insulin glargine and insulin detemir in the basal regimen for naïve insulin patients with type 2 diabetes mellitus (T2dm) in malaysia. *Clin Outcomes Res*. 2020;12:333-343. doi:10.2147/CEOR.S244884
23. Khairunnisa, Rawitri K, Wiryanto, Wahyuni S. Pengaruh Asuhan Kefarmasian Terhadap Outcome Klinis Dan Kualitas Hidup Pada Pasien Diabetes Melitus Tipe 2. *JFIOnline | Print ISSN 1412-1107 | e-ISSN 2355-696X*. 2021;13(2):118-128. doi:10.35617/jfionline.v13i2.18
24. Farshchi A, Aghili R, Oskuee M, et al. Biphasic insulin Aspart 30 vs. NPH plus regular human insulin in type 2 diabetes patients; a cost-effectiveness study. *BMC Endocr Disord*. 2016;16(1):1-9. doi:10.1186/s12902-016-0116-8
25. Lau E, Salem A, Chan JCN, et al. 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. *Cost Eff Resour Alloc*. 2019;17(1):1-13. doi:10.1186/s12962-019-0180-9

26. McEwan P, Foos V, Palmer JL, Lamotte M, Lloyd A, Grant D. Validation of the IMS CORE diabetes model. *Value Heal*. 2014;17(6):714-724. doi:10.1016/j.jval.2014.07.007
27. RI KK. *Pedoman Teknis Analisis Farmakoekonomi Di Fasilitas Kesehatan*.; 2016. doi:10.1088/1751-8113/44/8/085201
28. PERKENI. Pedoman Petunjuk Praktis Terapi Insulin Pada Pasien Diabetes Mellitus 2021. *Pb Perkeni*. Published online 2021:32-39.
29. Hirose T, Chen CC, Ahn KJ, Kiljański J. Use of Insulin Glargine 100 U/mL for the Treatment of Type 2 Diabetes Mellitus in East Asians: A Review. *Diabetes Ther*. 2019;10(3):805-833. doi:10.1007/s13300-019-0613-7
30. Wang L, Wei W, Miao R, Xie L, Baser O. Real-world outcomes of US employees with type 2 diabetes mellitus treated with insulin glargine or neutral protamine Hagedorn insulin: A comparative retrospective database study. *BMJ Open*. 2013;3(4):1-9. doi:10.1136/bmjopen-2012-002348
31. Rosenstock J, Fonseca V, Schinzel S, Dain MP, Mullins P, Riddle M. Reduced risk of hypoglycemia with once-daily glargine versus twice-daily NPH and number needed to harm with NPH to demonstrate the risk of one additional hypoglycemic event in type 2 diabetes: Evidence from a long-term controlled trial. *J Diabetes Complications*. 2014;28(5):742-749. doi:10.1016/j.jdiacomp.2014.04.003
32. Joseph JJ, Donner TW. Long-term insulin glargine therapy in type 2 diabetes mellitus: A focus on cardiovascular outcomes. *Vasc Health Risk Manag*. 2015;11:107-116. doi:10.2147/VHRM.S50286
33. Wolnik B, Wiza D, Szczepanik T, Syta A, Klupa T. Switching from Neutral Protamine Hagedorn Insulin to Insulin Glargine 300 U/mL Improves Glycaemic Control and Reduces Hypoglycaemia Risk: Results of a Multicentre, Prospective, Observational Study. *J Diabetes Res*. 2020;2020:0-7. doi:10.1155/2020/8751348
34. Bonadonna RC, Mauricio D, Müller-Wieland D, et al. Impact of Age on the Effectiveness and Safety of Insulin Glargine 300 U/mL: Results from the REALI European Pooled Data Analysis. *Diabetes Ther*. 2021;12(4):1073-1097. doi:10.1007/s13300-021-01030-0