

WILLINGNESS-TO-PAY FOR INSULIN IN DIABETES TREATMENT: A SYSTEMATIC REVIEW AND META-ANALYSIS

Le Thi Kieu Oanh*, Tran Thi Ngoc Van*, Hoang Thy Nhac Vu*

ABSTRACT.

Background: Insulin treatment is necessary for all patients with type 1 diabetes and a subset of patients with type 2 diabetes. However, lifetime insulin treatment is relatively costly that has put a heavy financial burden on insulin-dependent diabetics. Several studies thus have been conducted widely to estimate diabetes patients' willingness to pay (WTP) for insulin therapies worldwide. This study aimed to derive the diabetes patients' WTP for insulin therapy from the results of previous research studies.

Methods: A systematic review and meta-analysis of diabetes patients' WTP for insulin was conducted. All studies were searched and derived from PubMed combined with MeSH, Cochrane library combined with MeSH, ScienceDirect, and Springer Nature. The WTP values were estimated for three different types of insulin, including short-acting, rapid-acting insulin; long-acting, slow-acting insulin, and mixed insulin. Review Manager 5.1.4 software was used to conduct the meta-analysis. **Results:** Twelve studies were identified by the systematic review, in which eight studies were eligible for a meta-analysis. Most studies were conducted in high-income countries (83.3%), mainly in America (41.7%) and Europe (33.3%). The insulin formulation with the highest mean WTP value was Humalog Mix25 insulin, which was recorded at 410.42 USD per month in the UK and more than 120 USD per month in France, Italy, Spain, and Germany; while most of the other insulin formulations had mean WTP values less than 120

USD per month. Compared to diabetes patients, general populations were willing to pay less for insulin, which was observed in the case of Humalog Mix25 insulin (mean 95.77 USD per month vs 205.89 USD per month) and inhaled insulin (mean 50.43 USD per month compared to more than 120 USD per month). The meta-analysis showed the WTP value for insulin was 74.15 USD per month (95% CI; 55.82 - 92.48).

Conclusion: This study showed a comparison of WTP values for different insulin formulations worldwide. The mean WTP value for insulin derived from all previous research may provide an initial understanding of the individuals' preference and WTP. This information could contribute to the effort of managing diabetes and reducing the financial burden of this chronic disease.

Keywords: *Willingness to pay, insulin, diabetes, systematic review, meta-analysis.*

1. INTRODUCTION

The burden of diabetes management has become a pressing concern to the healthcare system of several countries. With a mortality rate ranking at third, diabetes has become one of the top ten causes of death worldwide [1-2]. The statistics of the International Diabetes Federation reported that there were 463 million adults aged from 20-79 years old living with diabetes in 2019 and predicted that the number of adult diabetics would reach 578 million in 2030 and 700 million in 2045 worldwide. Global diabetes health expenditures were anticipated to cost \$760 billion per year, reaching \$825 billion by 2030 and \$845 billion by 2045 due to the growing number of people with diabetes and the escalating prices of medical goods and services [3].

*University of Medicine and Pharmacy, Ho Chi Minh City

Responsible person: Hoang Thy Nhac Vu

Email: hoangthynhacvu@ump.edu.vn

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As a chronic disease, diabetes requires lifetime medications and the treatment goal is to avoid major morbidity and mortality and to reduce the risk of related complications by optimal glycemic control [4]. Diabetes medications are classified into insulins and non-insulins. Insulin-dependent diabetics, who are either with type 1 diabetes or with type 2 diabetes and failures to non-insulin therapies, benefit from insulin therapies. Compared to non-insulins, insulins are relatively costly since the doses must be tailored to each patient and the administration requires special devices. Additionally, among insulins, newer formulations such as rapid-acting insulin analogs have been provided at a significantly higher price. The financial burden of insulin thus has become more intolerable for insulin-dependent diabetics in particular and the healthcare system as a whole.

Several studies were conducted to estimate the willingness to pay (WTP) for insulin therapies to understand patients' preferences. This information could support the effort of reducing the financial burden for insulin-dependent diabetics. Doctors could find an optimal treatment approach for each individual patient, while policymakers could efficiently offer price negotiations and allocate resources for insulins marketed in their countries.

This systematic review and meta-analysis study was carried out to derive the patients' WTP for insulin from previous studies worldwide.

II. METHOD

Search strategy: This study was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure1) [1]. Four electronic databases, including

PubMed combined with MeSH, Cochrane library combined with MeSH, ScienceDirect, and SpringerNature were used to find all *original research* studies that reported the diabetes patients' WTP for insulin which were written in English, free full-text, and published till August of 2021.

The PICO approach was used to choose search terms from the list of medical subject headings (MeSH). The final search formula was ((Willingness to pay" OR "Willingness-to-pay" OR "WTP" OR "Discrete choice analysis" OR "Contingent Valuation Method" OR "Patient Preference" OR "Choice Behavior" OR "Surveys and Questionnaires" OR "Financing, Personal") AND ("Diabetes" OR "Diabetic" OR "Diabetes Mellitus" OR "Diabetes Mellitus, Type 1" OR "Diabetes Mellitus, Type 2" OR "Insulin")). The search range was in the titles and summaries of published studies.

The study selection process followed the PRISMA diagram and the quality of selected studies was evaluated by the PREFS checklist [1, 2]. There were 7644 studies identified from applying the search formula in all four databases. Duplicate removing and screening process narrowed down to 79 full-text studies. Twelve studies were eligible for the systematic review, in which eight studies were eligible for the meta-analysis.

Statistical methods: In this review, all the studied WTP values were uniformly presented as a mean value with a 95% confidence interval (CI). For WTP values which had been reported as a mean (\pm SD) or a mean (\pm SE), the following formulas were used to convert SD and SE to 95% CI: $SD = SE * \sqrt{N}$; $95\%CI = \bar{X} \pm Z * \frac{SD}{\sqrt{N}}$; (*SD: standard deviation; SE: standard error; 95%CI: 95% confidence intervals; \bar{X} : mean of WTP value; Z=1,96; N: sample size*). For WTP values which had been reported only

for subgroups, an average approach was used to obtain the WTP value for the total sample. All the mean WTP values with 95% CI then were converted to USD and VND values in 2021 using exchange rates and the medical consumer price index (CPI) to make comparisons [3].

Microsoft Excel was used to develop the search strategy and search formula. Review Manager 5.1.4 software was used to perform the meta-analysis with a random effect model, following the recommendation from the Cochrane Collaboration [4]. The meta-analysis results were presented by a forest plot diagram and tested for heterogeneity by the I² test, in which the heterogeneity was relatively high if I² >50%.

III. RESULTS

Characteristics of selected studies:

Twelve studies on estimating WTPs for insulin were included in the systematic

review, in which seven studies were published before 2010 and five studies were published since 2011. Ten studies were conducted in high-income countries which were classified according to the New World Bank country categories by income level [5]. Type 2 diabetes patients were the most popular subject of interest. (Table 1)

Willingness to pay for insulin: Of twelve selected studies, 41.7% estimated the WTP for long-acting and slow-acting insulin, 33.3% for rapid-acting and short-acting insulin, and 25.0% for mixed insulin (Table 2). Eight studies (fifteen data) were meta-analyzed on WTP for insulin. The results showed that the overall mean WTP for insulin was 74.15 USD per month (95% CI; 55.82 - 92.48). The results of the heterogeneous assessment showed a relatively high heterogeneity (I²=99%, df=14, and p<0.05). (Figure 2)

Table 1. Characteristics of twelve WTP studies for insulin worldwide published till August 2021

Characteristics of studies	Insulin		
	Short-acting, rapid-acting insulin (n=4 studies)	Long-acting, slow-acting insulin (n=5 studies)	Mixed insulin (n=3 studies)
Year of publication			
1998-2010	[6-9]	[10]	[11,12]
2011-2021		[13-16]	[17]
Sample size			
≤100	[6, 8]		[11]
101-500	[7, 9]	[10, 13, 15]	[12]
501-1000			[17]
> 1000		[14, 16]	
Countries			
The United State	[9]		
Sweden		[14,15]	
Canada	[7,8]	[10]	[11]
Australia	[6]		
United Kingdom		[13]	
India			[17]
Multinational		[16]	[12]

Continents			
Europe		[13-15]	[12]
America	[7-9]	[10]	[11]
Asia			[17]
Australia	[6]		
Multi-continent		[16]	
Countries by income level			
High income	[6-9]	[10,13-15]	[11,12]
Low and middle income		[16]	[17]
Participants in the survey			
Diabetes patients	[6, 8, 9]	[9, 13]	
Type-2 diabetes patients		[14,16]	[12,17]
General population	[7]	[15]	[11]

Table 2. Willingness to pay (WTP) values of insulin (USD 2021 and VND 2021)

Types of insulin	Population (year of study)	Mean WTP (95% CI) per month (USD)	Mean WTP (95% CI) per month (VND)
Short-acting, rapid-acting insulin			
Insulin lispro	83 patients in Australia (1998) [6]	41.80 (40.10 - 43.50)	967,043 (927,724 - 1,006,362)
Inhaled insulin	96 patients in Canada (2005) [7]	205.89 (179.12 - 232.66)	4,763,215 (4,143,902 - 5,382,528)
	120 individuals of general population in Canada (2007) [8]	95.77 (84.63 - 106.91)	2,215,639 (1,957,843 - 2,473,435)
	1103 patients in US (2009) [9]	77.40 (*)	1,790,624 (*)
Long-acting, slow-acting insulin			
Oral long-acting, slow-acting insulin	227 patients in Canada (2008) [10]	27.83 (0.11 - 55.55)	643,951 (2,514 - 1,285,149)
	252 patients in UK (2011) [13]	31.07 (*)	718,806 (*)
Insulin detemir	333 patients in Sweden (2012) [14]	1.88 (*)	43,526 (*)
Basal insulin	646 patients in North American countries (2017) [16]	77.38 (47.84 - 106.92)	1,790,109 (1,106,720 - 2,473,594)
	1537 patients in South American countries (2017) [16]	51.58 (31.99 - 71.17)	1,193,406 (809,545 - 1,646,518)
	1575 patients in European countries (2017) [16]	64.81 (44.36 - 86.26)	1,499,408 (1,026,380 - 1,995,625)
	333 patients in Sweden (2012) [14]	43.23 (*)	1,000,220 (*)
	987 individuals of general population and 1034 patients in Sweden (2016) [15]	41.60 (*)	962,511 (*)
Mixed insulin			
Humalog Mix25 insulin	53 patients in France (2004) [12]	310.06 (107.76 - 512.36)	7,173,150 (2,492,991 - 11,853,449)
	60 patients in Germany (2004) [12]	267.44 (122.24 - 412.64)	6,187,288 (2,828,125 - 9,546,426)

	56 patients in Italy (2004) [12]	120.32 (38.79 - 201.85)	2,783,669 (897,437 - 4,669,800)
	60 patients in Spain (2004) [12]	316.88 (187.26 - 446.50)	7,330,948 (4,332,324 - 17,447,031)
	61 patients in UK (2004) [12]	410.42 (177.00 - 648.84)	9,495,155 (4,094,896 - 132,488,581)
	80 individuals of general population in Canada (2000) [11]	50.43 (39.94 - 60.94)	1,166,768 (924,055 - 1,409,793)
Humulin 30/70 insulin	80 individuals of general population in Canada (2000) [11]	2.85 (2.57 - 3.13)	65,934 (59,394 - 72,474)
Biphasic Insulin Aspart 30/70	505 patients in India (2021) [17]	15.69 (10.71 - 20.67)	362,930 (247,710 - 478,151)

(*) 95% CI was not available

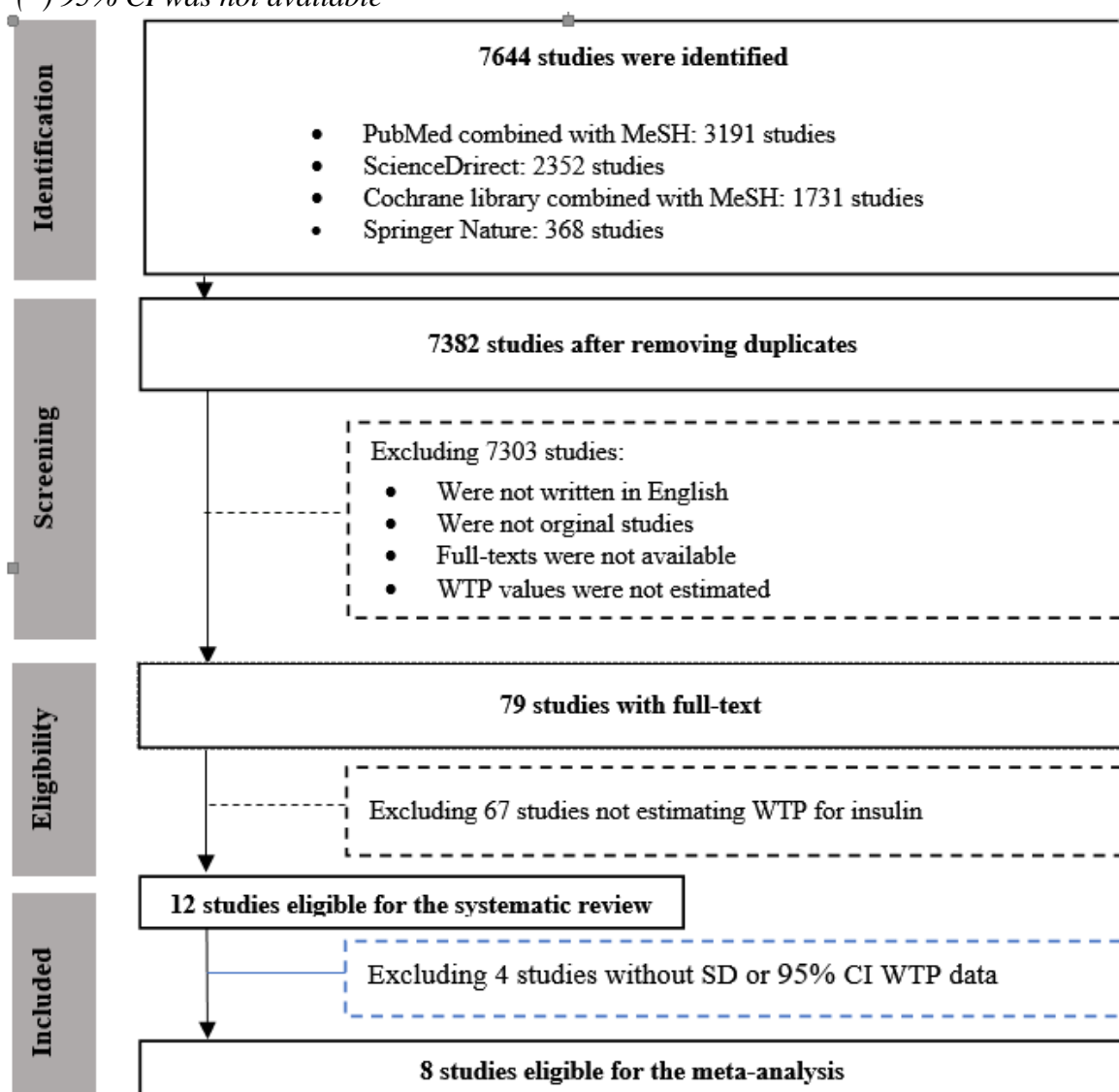


Figure 1. The systematic review study selection process following the PRISMA diagram

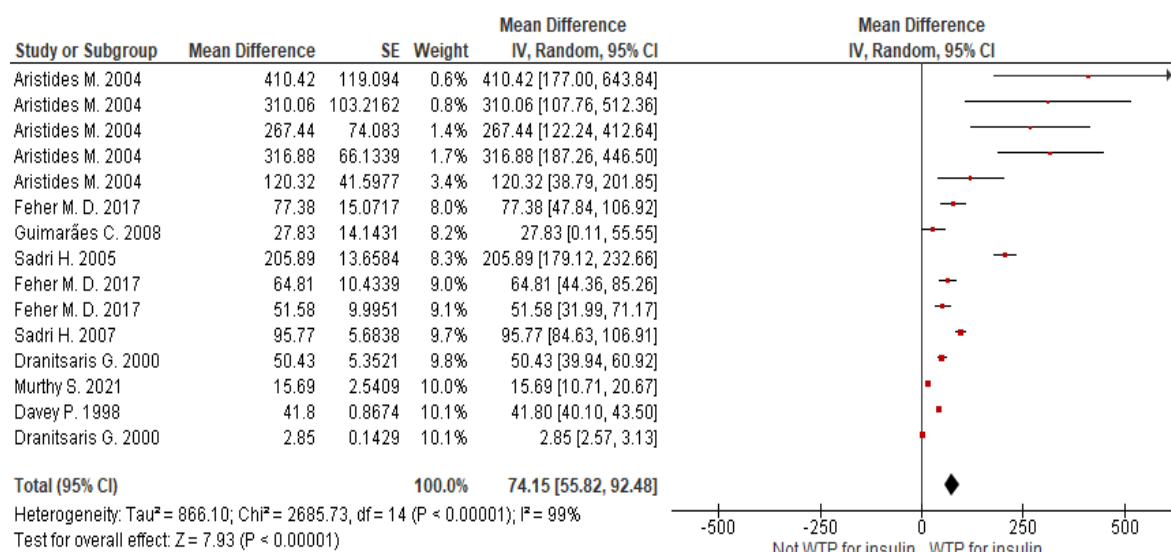


Figure 2. Random effect model of the overall mean WTP for insulin with 95% confidence interval

IV. DISCUSSION

This review included a total of twelve studies on estimating WTP for insulin. The majority of studies were published before 2010 (58%), with a focus on estimating the WTP for the short-acting and rapid-acting insulin (57%), which showed a major concern on the cost of this very first insulin formulation during that period of time [18]. The interest in estimating WTP for insulins then was completely shifted into the newer insulin formulations, in which estimating WTP for the long-acting, slow-acting insulin accounted for 80% of the total studies published since 2011. While only two studies were published in low and middle income countries, there were 10 studies published in high income countries, which may imply differences in the research interest and resources.

This systematic review showed that the insulin formulation with the highest mean WTP value was Humalog Mix25 insulin, which was estimated at 410.42 USD per

month in the UK and more than 120 USD per month in France, Italy, Spain, and Germany [12]. This could be explained partially by the significantly higher effectiveness of Humalog Mix25 insulin which was better postprandial glycemic control and lower incidence of nocturnal hypoglycemia [19]. In contrast, estimated mean WTPs of insulin formulations including insulin lispro, oral long-acting, slow-acting insulin, Insulin detemir, basal insulins, Humulin 30/70 insulin, and Biphasic Insulin Aspart 30/70 were all less than 120 USD per month [6, 10-11, 13-17]. In Canada, compared to diabetes patients, general populations were willing to pay less than half for inhaled insulin (mean 95.77 USD per month vs 205.89 USD per month) [7, 8]. A similar result was observed that general population was willing to pay less than patients (mean 50.43 USD per month compared to more than 120 USD per month) when comparing the mean WTPs of Humalog Mix25 insulin among countries [11, 12]. The lowest mean WTP values were 1.88 USD per month for Insulin detemir in

the case of 333 Sweden's patients in 2012 and 2.85 USD per month for Humulin 30/70 insulin in the case of 80 individuals of Canada's general population in 2000 [11,14].

The meta-analysis showed that participants were willing to pay for insulin rather than non-insulin and the mean WTP value derived was 74.15 USD per month. However, studies showed a relatively high heterogeneity with $I^2 > 99\%$ and $p < 0.05$. This suggested further research to carry out subgroup analyses with more consistency to gain a more precise overall effect from the random effects model.

V. CONCLUSION

This study provided an overview of WTP values for different insulin formulations worldwide. The mean WTP value for insulin derived from all previous research may provide an initial understanding of the individuals' preference and WTP. This information could contribute to the effort of managing diabetes and reducing the financial burden of this chronic disease.

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