Research Article

Pharmacoeconomic Evaluation: Cost Effectiveness Analysis of Oral Antidiabetic Therapy in A Tertiary Care Hospital

Sereena Saju*[1], Fedrin V Varghese[1], Deena R S[1], Nivetha N R[1], Dr. Samhitha Chetty[2], Dr. K. Uma Mahesh[3]
PharmD Interns[1], Assistant Professor[2], Consultant Diabetologist (MBBS, MDRC)[3]
K. K. College of Pharmacy, The Tamil Nadu Dr. M.G.R Medical University, Chennai – 600122, India.[1,2]
Vijaya Group of Hospital, Vadapalani, Chennai – 600026, India.[3]
***Corresponding author's E-mail:** connectsereena@gmail.com

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ABSTRACT

The objective of the study was to assess the cost effectiveness of oral antidiabetic therapy in type 2 diabetes mellitus in a tertiary care hospital. A prospective observational study was conducted in a population of approximately150 sample for 6 months in patients receiving antidiabetic therapy. The datas were collected using a specially designed data entry form including, patient specific HbA1C and other glycaemic values along with the prescription details of the patient with a follow up to determine the most cost- effective drug among oral hypoglycaemic agents using the Incremental Cost Effectiveness Ratio (ICER). Glimepiride was found to be the most cost-effective drug with lowest ICER of Rs 1182.273 among monotherapy. Among multiple drug therapy (1+1), Voglibose as an add on to Glimepiride while Metformin added to a fixed dose combination of Metformin and Glimepiride were found to be the most cost-effective drug with the lowest ICER of Rs. 2217.6 and Rs 369 respectively. Among multiple drug therapy (1+2) Voglibose and Glimepiride added on to Metformin alone and, Glibenclamide and Voglibose added on to the fixed dose combination of Metformin and Teneligliptin were found to be the most cost-effective drug with the lowest ICER of Rs 3085.71 and Rs 184.5, respectively. The most cost-effective drug among FDC was found to be Metformin + Glimepiride with the lowest ICER of Rs 1642.48. Among fixed dose triple combination of Metformin + Glimepiride + Pioglitazone was found to be dominant. Most of the patients were receiving monotherapy (41.33%) followed by FDC (34.66%).

Keywords: Pharmacoeconomics, Oral Antidiabetic therapy, Cost-effectiveness, Incremental Cost-Effective Ratio (ICER).

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INTRODUCTION

Diabetes is one of the fastest status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease. In 2000, India (31.7 million) aced the world with the highest number of people with diabetes mellitus followed by China (20.8 million) with the United States (17.7 million) in second and third place respectively.[1,2]

The International Diabetes Federation (IDF) predicts the number of patients with Diabetes Mellitus (DM) will increase to 380 million by 2025.[3] According to American Diabetes Association (ADA) criteria, the prevalence of DM was 4.7% in the urban areas whereas 1.9% in the rural areas. [4] It is estimated that developing countries will bear 77% of the global burden of the DM epidemic in the 21st century as a result of population growth, consumption of unhealthy diets, obesity, and sedentary lifestyles.[5,6]

Due to large population, India has been the world's largest population living with DM after China. The growing epidemic of type 2 DM coerced the total health expenditure of such population to a peak level.[7] Therefore, the application of economic evaluation methods to healthcare products and services, especially pharmaceuticals including the costs and its outcomes may reduce the healthcare burden on patients with Diabetes Mellitus.[8]

Pharmacoeconomics is an innovative method that evaluates the clinical, economic and humanistic aspects of pharmaceutical products, involving cost minimization analysis (CMA), cost-effectiveness analysis (CEA), cost–utility analysis (CUA), and cost–benefit analysis (CBA). It mainly focuses on the costs and outcomes of drug therapy and provide a basis for resource allocation and utilization. Hence, the need for pharmacoeconomics is increasingly emerging in health policy decision-making especially in developing countries like India.[9] The main aim of this study was to determine the most cost-effective oral antidiabetic therapy utilized in a tertiary care hospital using a statistical analysis of incremental cost-effectiveness ratio (ICER). Other objectives of this study were to monitor prescription pattern and assessing the medication adherence to oral anti-diabetic therapy.

MATERIALS AND METHODS

This prospective cost-effective study was conducted for 6 months in both inpatients and outpatients with Type 2 DM in a 750 bedded multispecialty hospital located at Vadapalani, Chennai. The study was approved by the Institutional Ethical Committee of Vijaya Hospital. Nearly about 245 Type 2 DM patients were interviewed and based on inclusion and exclusion criteria, 150 patients were recruited in our study after getting the patient consent. The required data including patient demographic details, specific HbA1C and other glycaemic values along with the prescription details of the patient were collected in a specially designed data entry form during the initial visit. The second follow-up was done after 3 months via phone call to the particular individual patients for review and again the HbA1C values and other glycaemic values were noted in the specified data entry form.

The study included patients of age between 20 – 80 years of both genders, diagnosed with type 2 DM prescribed with oral hypoglycaemic agents. Pregnancy and Lactating women, patients on insulin therapy, patients on steroid medications, patients with lifestyle modifications alone and patients diagnosed with a history of greater than five years of Type 2 DM were excluded from the study. The collected datas were analysed and the adherence level of the patients during the initial visit and the second follow-up were categorized into low, medium and high adherence by using Modified Morisky Adherence Scale.

The data was interpreted using ICER quadrant plane and the report was developed using ICER decision matrix.

Statistical analysis

The HbA1C level before and after the drug treatment was expressed as Mean ± SD. Paired student t- test was used to analyse the statistical difference between the HbA1C reductions with various oral hypoglycaemic agents. A P-value of <0.05 was considered as statistically significant.

RESULTS AND DISCUSSION

Patient Demographics

The data collected from 150 diabetic patients enrolled into our study was analysed and categorized according to the patient demographics. Among the study group, the maximum number of patients 50 (33.3%) were in the age group of 61-70 years. In a study by Asiimwe D et al [10], reported a similar finding where diabetes was found to be high in the age group of 61-65 with 65% followed by the age group of 51-55 with 30.4%. The male patients 89 (59.33%) were more predominant than female patients 61 (40.66%), identical to a study by Grant JF et al [11], where higher prevalence of type 2 DM was seen in men. (Table 1)

Co- Morbidity Assessment

The condition Diabetes Mellitus has many comorbidities such as hypertension, Kidney diseases, heart diseases, dyslipidaemia, coronary artery disease etc. Among these, Coronary Artery Disease (CAD) (21.33%) was the most predominant comorbid condition in our study population, followed by Hypertension 12 (8.8%) and Chronic Kidney Disease in 8 (5.33%) (Table 2). These findings are similar to a study conducted by Ferrannini G et al [12], where CAD (27.2%) was considered to be more prevalent followed by Hypertension (12.24%) among participants with T2D than those without diabetes.

Table 1: Patient Demographics

Demographics		No. of Patients (n=150)	Percentage (%)
Gender	Male	89	59.33%
	Female	61	40.66%
Age	21-30	2	1.33%
	31-40	6	4%
	41-50	27	18%
	51-60	47	31.33%
	61-70	50	33.33%
	71-80	17	11.33%

Table 2: Comorbidities of Diabetes Patients

Co-morbidities	No of Patients (n=150)	Percentage (%)
CAD	32	21.33%
Hypertension	12	8.00%
CKD	8	5.33%
COPD	8	5%
Dyslipidaemia	7	4.66%
Hypothyroidism	5	3.33%
Anaemia	6	4%
ACS	4	2.66%
Angina	3	2%
Cardiomyopathy	3	2%
Others	62	41.33%

Abbreviations: CAD- Coronary Artery Disease; CKD- Chronic Kidney Disease; COPD- Chronic Obstructive Disease; ACS- Acute Coronary Syndrome

PHARMACIST ASSESSMENT OF DIABETES PATIENTS

Medication Adherence

The level of medication adherence was monitored before and after the oral antidiabetic therapy using Modified Morisky Adherence Assessment Scale. During the initial visit, about 81 (54%) of the diabetic patients in the study were highly adherent to the drug therapy, 51 (34%) were moderately adherent and remaining 18 (12%) were having low adherence. Whereas, on day 90 (second follow-up), about 82 (54.66%) of the diabetic patients in the study were highly adherent to the drug therapy, 56 (37.33%) were moderately adherent and remaining 12 (8%) were

having low adherence. It was observed that the percentage of people who were less adherent during the initial visit has decreased from 12% to 8% on second follow-up. Even though, this was a small percentage difference, it shows that a significant change in the level of adherence can be done through continuous patient counselling interventions in patients (Figure 1). This result contradicts a study by Sefah IA et al [13], where Adherence to oral hypoglycemic drugs among T2DM patients was sub-optimal.

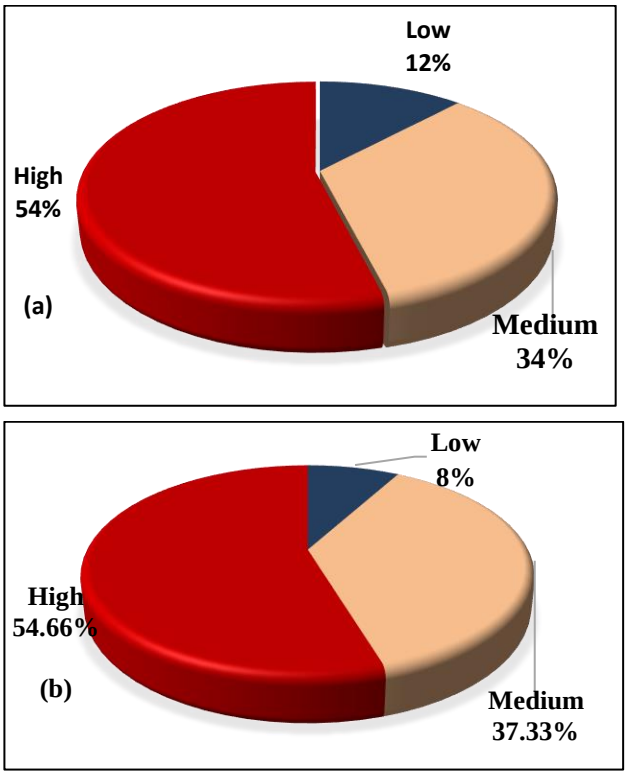

Figure 1: Medication Adherence (a) Before the treatment (b) After the treatment

Drug Prescription Pattern

The drug prescription pattern of oral hypoglycaemic agents among the 150 diabetes patients was categorized into 4 groups: monotherapy, multiple drug therapy [add on (1+1, 1+2); fixed dose (1+1, 1+2)], fixed dose double combination (FDDC) and fixed dose triple combination (FDTC).

- In the category of monotherapy 62 (41.33%), Metformin in 36 (58.06%) patients was highly prescribed. A similar finding was observed in a study by Rojas LB et al.[14]
- Among multiple drug therapy (MDT) 52 (34.66%), Glimepiride and Glipizide were equally prescribed as an add on to Metformin in 2 (16.66 %) patients, as supported by Hassan MH et al [15], in his study.
- Teneligliptin was highly prescribed as an add on to Gliclazide in 2 (16.66 %) patients in case of MDT (1+1), is in contradiction with a study by Kumar VN et al [16], where Teneligliptin added to Pioglitazone was mostly prescribed. However, Metformin was prescribed as an add on to Metformin + Glimepiride in 6 (27.27%) patients among MDT-FDC (1+1).
- Glimepiride and Voglibose were prescribed as an add on to Metformin in 5 (45.45%) patients among MDT (1+2). Metformin and Voglibose were prescribed as an add on to Metformin + Glimepiride in 3 (42.85%) patients among MDT-FDC (1+2). These findings are consistent with a study by Murthi K et al [17].
- A fixed dose of Metformin + Glimepiride was prescribed among fixed dose double combination in 19 (63.33%) patients. These findings corelates to a similar study conducted by Tamilselvan et al [18].
- Metformin + Glimepiride + Voglibose among fixed dose triple combinations in 4 (66.66%) patients was prescribed, which is in agreement with the study results obtained by Kulkarni Dhananjay et al [19], where a FDC of Metformin, Glimepiride and Voglibose was prescribed.

Incremental Cost Effectiveness Ratio (ICER) Analysis

The incremental cost-effectiveness ratio (ICER) is a statistic used in cost-effective analysis to determine the cost-effectiveness of a health care intervention. It was calculated using ICER formula and the result was based on ICER quadrant plane and ICER decision matrix.

Considering HbA1C reduction, Metformin among monotherapy, shows the maximum HbA1C reduction. The statistical analysis of comparison of mean Hba1c reduction of monotherapy was done, in which there was a significant difference between the HbA1C level of the patient before and after the Glimepiride (*p0.008) treatment with lowest ICER (1182.2) for 1% HbA1C reduction, hence found to be the most effective drug when compared with other drugs among monotherapy (Table 3). These findings are in accordance with a study conducted by Zhu et al [20] which concluded that both Metformin and Glimepiride were effective in controlling glycemic levels.

Among multiple drug therapy (1+1), considering HbA1C reduction, Metformin as an add on to Glibenclamide and Voglibose as an add on to Glimepiride shows the maximum HbA1C reduction. The statistical analysis of comparison of mean HbA1c reduction of multiple drug therapy (1+1) did not result in any significant association. However, Voglibose as an add on to Glimepiride was found to be the most cost-effective drug with the lowest ICER of Rs. 2217.6 for 1% HbA1C reduction. In a similar study by Murthi K et al [17], where Voglibose added to Glimepiride showed a very significant benefit in controlling the glucose levels and considered to be most cost-effective agent.

Similarly, in multiple drug therapy among FDC (1+1), considering HbA1C reduction, Pioglitazone and Gliclazide as an add on to Metformin and Glimepiride fixed dose combination, showed a maximum HbA1C reduction. Our study observations support the results proposed by A. Paneerselvam et al [21], where Pioglitazone improved cardiovascular risk factors more effectively than gliclazide when given in combination-based therapies in addition to

glycemic benefits. The statistical analysis of comparison of mean HbA1c reduction was done, in which there was a significant difference between the HbA1C level of the patient before and after the Metformin (p 0.038) and Vildagliptin (0.003) added on to the fixed dose combination of Metformin and Glimepiride treatment respectively. However, Metformin as an add on to Metformin and Glimepiride FDC was found to be the most cost-effective drug with ICER of Rs 369 for 1% HbA1C reduction. (Table 4)

Table 3: Comparison of ICER of Monotherapy

Drugs	Cost for 3 months (Rs)	Mean ± SD of HbA_1C		Reduction of HbA_1C (%)	P value	IC	IE	ICER
		Before Treatment	After Treatment					
Glipizide	54	8.1 ± 1.3	7.8 ± 0.9	0.23	0.725	-	-	-
Glimepiride	314.1	7.6 ± 0.6	7.0 ± 0.6	0.45	0.008*	260.1	0.22	1182.2
Teneligliptin	445.5	7.9 ± 0.7	7.4 ± 0.8	0.55	0.057^{ns}	131.4	0.1	1314
Sitagliptin	4050	7.9 ± 1.4	7.2 ± 1.4	0.7	-	3604.5	0.15	24030

IC- Incremental Cost; **IE**- Incremental Effect; ***p** < 0.05 = significant, **ns** – non significant

Table 4 - Comparison of ICER of Multiple Drug Therapy (1+1)

Drugs	Add on Drug	Cost for 3 months (Rs)	Mean ± SD of HbA1C		Reduction of HbA_1C (%)	P-Value	IC	IE	ICER
			Before Treatment	After Treatment					
Multiple Drug Therapy (1+1)									
Metformin	Glibenclamide	159.3	8.9 ±0.1	7.6 ±0.1	0.8	-	-	-	-
Glimepiride	Voglibose	1268.1	9.5 ±0.1	8.2 ±0.1	1.3	-	1108.8	0.5	2217.6
Multiple Drug Therapy Among FDC (1+1)									
Metformin + Glimepiride	Pioglitazone	531	8.3 ±2.3	7.3 ±1.8	1.05	0.204^{ns}	-	-	-
Metformin + Glimepiride	Metformin	567.9	8.9 ±1.6	7.8 ±1.2	1.15	0.038*	36.9	0.1	369

IC- Incremental Cost; **IE**- Incremental Effect; ***p** < 0.05 = significant, **ns** – non significant

Among multiple drug therapy (1+2), considering HbA_1C reduction, Glimepiride and Pioglitazone as an add on to Metformin, shows the maximum HbA_1C reduction, as corelated to a study by A. Paneerselvam et al [21]. The statistical analysis of comparison of mean HbA_1C reduction of multiple drug therapy (1+2) was done, in which there was a significant difference between the HbA_1C level of the patient before and after Voglibose and Glimepiride (p 0.002) treatment added on to the Metformin with the lowest ICER of Rs 3085.71 for 1% HbA_1C reduction and hence, found to be the most effective drug. A similar result was observed by Murthi K et al [17], in his study.

Similarly, in multiple drug therapy among FDC (1+2), considering HbA1C reduction, Metformin and Voglibose as an add on to FDC Metformin and Glimepiride, shows maximum HbA_1C reduction. These findings are in coherence to a study by Dr. Jindal et al [22], which concluded that addition of voglibose to FDC Metformin and Glimepiride showed a significant reduction in FBG, PPBG and HbA_1C (glucose triad). The statistical analysis of comparison of mean HbA_1C reduction of multiple drug therapy among FDC (1+2) was done, in which there was a significant difference between the HbA_1C level of the patient before and after Sitagliptin and Metformin (p 0.025) was added on to the FDC of Metformin and Glimepiride treatment. However, Glibenclamide and Voglibose added on to the FDC of Metformin and Teneligliptin was found to be the most cost effective with the lowest ICER of Rs 184.5 for 1% HbA1C reduction (Table 5). These study observations are in accordance to a study conducted by Gupta CN et al. [23]

Considering HbA1C reduction, Double Fixed Dose Combination (FDC) of Metformin and Glipizide, shows the maximum HbA1C reduction. Statistical analysis of comparison of mean HbA1c reduction of double FDC was done, in which there was a significant difference between the HbA1C level of the patient before and after Metformin + Glimepiride (*p 0.001) and Metformin + Glibenclamide (*p 0.026) treatment. However, Metformin + Glimepiride was found to be the most cost effective with lowest ICER of Rs 1642.48 for 1% HbA1C reduction among other double FDC oral hypoglycaemic agents (Table 6). These results correlate to a study conducted by Hye-soon Kim et al [24] in which the fixed dose combination of Metformin and Glimepiride was found to be most cost-effective.

Considering HbA_1C reduction, Triple Fixed Dose Combination of Metformin + Gliclazide + Pioglitazone, shows the maximum HbA_1C reduction. Statistical analysis of comparison of mean HbA_1C reduction of FDTC did not result in any significant association. However, Metformin + Gliclazide + Pioglitazone found to be dominant among other triple FDC oral hypoglycaemic agents (Table 7). These findings are not in coherence with a study conducted by Arif A. Faruqui et al [25], where a fixed dose combination of Voglibose + Glimepiride + Metformin provides effective glycemic control in a safe and well tolerated manner.

Table 5: Comparison of ICER of Multiple Drug Therapy (1+2)

Drugs	Add on Drug (1)	Add on Drug (2)	Cost for 3 month (Rs)	Mean ± SD of HbA_1C		Reduction of HbA_1C (%)	P-value	IC	IE	ICER
				Before treatment	After treatment					
Multiple Drug Therapy (1+2)										
Metformin	Glimepiride	Pioglitazone	531	10.±0.1	8.5 ± 0.1	1	-	-	-	-
Metformin	Glimepiride	Voglibose	1395	9.2 ± 0.6	7.9 ± 0.5	1.28	0.002*	864	0.28	3085.7
Metformin	Gliclazide	Sitagliptin	4653	8.9 ± 0.1	7.9 ± 0.1	1.3	-	3258	0.02	16290
Glimepiride	Vildagliptin	Empagliflozin	7760.7	9.8 ± 0.1	8.7 ± 0.1	1.4	-	3107.7	0.1	31077
Multiple Drug Therapy among FDC (1+2)										
Metformin+ Glimepiride	Voglibose	Metformin	1521.9	7.9 ± 0.3	6.2± 0.3	1	0.104^{ns}	-	-	-
Metformin+ Teneligliptin	Voglibose	Glibenclamide	1558.8	9.7 ± 0.1	8.5± 0.1	1.2	-	36.9	0.2	184.5
Metformin+ Glimepiride	Metformin	Sitagliptin	4617.9	7.7 ± 0.1	6.4± 0.1	1.25	0.025*	3059.1	0.05	61182

IC- Incremental Cost; **IE**- Incremental Effect; ***p** < 0.05 = significant, **ns** – non significant

Table 6: Comparison of ICER of Double Fixed Dose Combination

Drugs	Cost for 3 months (Rs)	Mean ± SD of HbA_1C		Reduction of HbA_1C (%)	P-Value	IC	IE	ICER
		Before treatment	After treatment					
Metformin+ Glibenclamide	105.3	8.9 1± 1.10	8.40 ± 1.24	0.516	0.026*	-	-	-
Metformin+ Glimepiride	441	8.11± 1.16	7.51 ± 1.10	0.721	0.001*	335.7	0.2	1642.48
Metformin+ Voglibose	1080.9	8.65 ± 1.48	7.65 ± 1.20	1	0.125^{ns}	639.9	0.27	2293.98

IC- Incremental Cost; **IE**- Incremental Effect; ***p** < 0.05 = significant, **ns** – non significant

Table 7: Comparison of ICER of Fixed Dose Triple Combination

Drugs	Cost for 3 months (Rs)	Mean ± SD of HbA_1C		Reduction of HbA_1C (%)	P-value	IC	IE	ICER
		Before treatment	After treatment					
Metformin + Glimepiride + Voglibose	1395	7.4 ± 0.8	7.0 ± 0.7	0.325	0.452^{ns}	-	-	-
Metformin + Gliclazide + Pioglitazone	693	8.3 ± 0.4	7.0 ± 0.6	1.25	0.076^{ns}	-702	0.925	-758.91

IC- Incremental Cost; **IE**- Incremental Effect; ***p** < 0.05 = significant, **ns** – non significant

Since, Diabetes Mellitus is a chronic illness which requires prolonged medical care to prevent the risk of long-term complications and heavy burden of cost have greatly influenced the compliance of the patients thus contributes to deterioration of patient's quality of life. Therefore, this pharmacoeconomic study has analysed the overall aspects of an antidiabetic agents in a bid to provide evidence-based information that could be taken into consideration to alter the practice of irrational prescription of less cost-effective antidiabetics over more cost-effective OHAs.

CONCLUSION

Pharmacoeconomic evaluation should be encouraged to ensure the cost-effective therapy in diabetic patients. As per our results, Glimepiride may be considered as the most cost-effective monotherapy with the lowest ICER value in subjects with Type 2 Diabetes Mellitus.

Similarly, Glibenclamide and Voglibose added on to the fixed dose combination of Metformin and Teneligliptin can be considered as the most cost-effective therapy among all the multiple drugs therapy in our study settings.

For uncontrolled Type 2 Diabetes Mellitus, double fixed dose combination (FDC) of Metformin and Glimepiride can be considered a valuable option for the management of hyperglycaemia with respect to cost effectiveness. Treatment with triple FDC of Metformin, Glimepiride and Pioglitazone is found to be dominant rather than cost effective. Despite the significance results, the study also found that the percentage of people who were less adherent has decreased from 12% to 8%.

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