Scientific Research Publishing

Open Journal of Endocrine and Metabolic Diseases, 2019, 9, 21-33
http://www.scirp.org/journal/ojemd
ISSN Online: 2165-7432
ISSN Print: 2165-7424

Assessment of Safety and Effectiveness of Glaritus® (Wockhardt's Insulin Glargine) in a Prospective, Multi-Centric Post Marketing Observational Study in Nepalese Having Type 2 Diabetes Mellitus

Ansumali Joshi[1], Bhojraj Adhikari[2], Basant Tamrakar[3], Gaurav Puppalwar[4*], Agam Shah[4], Rishi Jain[4]

[1]Kathmandu Diabetes & Thyroid Centre Pvt. Ltd., Kathmandu, Nepal
[2]Pushpanjali Hospital, Bharatpur, Nepal
[3]Fishtail Hospital & Research Centre Pvt. Ltd., Pokhara, Nepal
[4]Medical Affairs, Wockhardt Ltd., Mumbai, India
Email: *Gpuppalwar@wockhardt.com

How to cite this paper: Joshi, A., Adhikari, B., Tamrakar, B., Puppalwar, G., Shah, A. and Jain, R. (2019) Assessment of Safety and Effectiveness of Glaritus® (Wockhardt's Insulin Glargine) in a Prospective, Multi-Centric Post Marketing Observational Study in Nepalese Having Type 2 Diabetes Mellitus. *Open Journal of Endocrine and Metabolic Diseases*, **9**, 21-33.
https://doi.org/10.4236/ojemd.2019.92003

Received: November 5, 2018
Accepted: February 24, 2019
Published: February 27, 2019

Abstract

Background: Nepal is one of the fastest urbanizing countries in South Asia and is facing the consequences of urban lifestyle leading to obesity and metabolic syndrome. Type 2 diabetes mellitus (T2DM) is currently a high-burden disease in Nepal with a prevalence of 8.4%. Of these 8% - 18% patients are on insulin and 42% patients were reported to have uncontrolled diabetes in the past year. This suggests a need for better therapy options in terms of efficacy and safety. The current study was designed to investigate the effects of Insulin glargine-based therapy in Nepalese with T2DM who could not achieve adequate glycemic control with oral and non-glargine-insulin therapy. **Methods:** This is a prospective, multi-centric, single arm and post marketing observational study to assess the safety and effectiveness of Glaritus® (Wockhardt's Insulin Glargine) in 52 T2DM patients from 3 (three) different study sites in Nepal (Bharatpur, Kathmandu and Pokhra) from September 2015 to December 2016. The primary objective of the study was to evaluate the safety of Glaritus®, mainly in terms of hypoglycemia, renal function tests and liver function tests. The secondary objectives were to evaluate the effectiveness of Glaritus® in terms of percentage of patients achieving HbA1c goal of less than 7%, mean changes in HbA1c & fasting plasma glucose (FPG) levels from baseline till the end of study. **Results:** 3.85% of subjects experienced hypoglycemia during first 3 months of therapy whereas 1.92% had similar expe-

rience in next 3 months of therapy. The mean HbA1c values reduced from 9.16% to 7.15% at the end of study. 21.05% of the enrolled subjects achieved the goal of HbA1c < 7% at the end of 3 months of therapy, whereas 52.5% achieved the target HbA1c at the end of 6 months of therapy. The mean FPG value of study population reduced from 239.94 mg/dl to 151.31 mg/dl at the end of study. There was no significant change in renal or liver functions during treatment. None of the subjects experienced any other adverse event (AE), thus indicating that Glaritus® was well tolerated by the study patients. **Conclusion:** In patients with type 2 diabetes mellitus inadequately controlled on oral hypoglycemic agents and/or insulin, initiation with Glaritus® significantly improved glycemic control with good tolerability and acceptability. This analysis in T2DM Nepalese patients shows that by significantly improving glycemic control while not increasing risk of hypoglycemia, Glaritus® provides safer basal insulin and may be suited to aggressive treatment regimens. From a societal perspective, it will help more patients reach the glycemic control target as recommended by the current treatment guidelines.

Keywords

Insulin Glargine, Type 2 Diabetes, Nepalese Patients, Hypoglycemia, Basal Insulin, HbA1c, Fasting Plasma Glucose, Post Marketing Surveillance

1. Introduction

1.1. Rising Burden of T2DM in Nepal

Asia is a home to four of the world's five countries with the largest diabetes burden—India topping the charts at 33 million cases, followed by China having 23 million cases, and Pakistan and Japan having 9 and 7 million cases, respectively [1]. The prevalence of diabetes in Nepal is not well characterized due to paucity of studies. But it is logical to assume that epidemiological profile of diabetes in Nepal must be very similar to its neighboring countries as they share lineage, culture and lifestyle profiles [2]. Gyawali *et al.* [3] evaluated the prevalence of diabetes in Nepal in a meta-analysis and systematic review for a 14-year duration (2000-2014). Pooled prevalence of type 2 diabetes was 8.4% (95% CI: 6.2% - 10.5%) and it differed significantly in urban (8.1%) and rural (1%) populations. Currently, Nepal is the fastest urbanizing country in South Asia with an average urban population growth rate of about 6 percent per year [4] and is facing the consequences of urban lifestyle leading to obesity and metabolic syndrome. Amongst the diabetic population in Nepal, 8% - 18% are on insulin [5] [6]. In a prospective study assessing the drug prescribing trend in 100 patients including 41 diabetic patients, insulin was included only in 2.5% of prescriptions [7]. In a study conducted by Sapkota *et al.* in 200 diabetic patients, 52% patients self-reported not knowing whether their diabetes was well-controlled and 42% had to seek help at least once within the last year for uncontrolled diabetes (in-

cluding hypo or hyperglycemia) [6]. The situation indicates towards potential for improving diabetes management by enhancing insulin utilization in Nepalese diabetic patients. As the representation from Nepal in global diabetes research and publications is not proportionate to the rising epidemiology, our study is a step forward in contributing to diabetes research representing Nepalese population.

1.2. Value of Intensive Glucose Control Early in the Natural Course of Diabetes

The aim of insulin therapy is to mimic the physiological secretion of insulin so that it accommodates both fasting and post-prandial requirements. The UK Prospective Diabetes Study (UKPDS) established that initiating intensive glucose control at the time of diagnosis leads to significant reduction in the risk of cardiovascular and microvascular complications [8]. But it must be done with minimal risk of hypoglycemia. Development of long-acting insulin analogs represented a promising step forward in meeting this requirement. Insulin Glargine now represents a reference basal insulin compared to which future developments in long-acting insulin analogs are measured [9] [10] [11]. The updated clinical practice is to initiate insulin therapy early as part of "treat-to-target" strategy when ≥2 oral anti-diabetic drugs are not able to meet the individualized glycemic targets currently recommended for T2DM management [12]. But in real-world, clinical inertia prevails towards early insulinization due to fear of hypoglycemia [13]. Weight gain and the limited flexibility of some insulin regimens [14] may contribute to omission of injections, prolonged continuation of inadequate protocol posing long-term diabetes complications.

1.3. The Characteristics of Insulin Glargine

There are several options available for initiating insulin therapy. A basal peak-less insulin supply, offering a long duration of action, is desirable. Long-acting insulin analogs like glargine have been developed in such a way that it releases insulin at a reduced rate from its depot, resulting in flat pharmacokinetic profile for 24 h. Once-daily basal insulin offers the patient practicality and simplicity of use, hence is the most convenient insulin initiation strategy.

Insulin glargine is the most commonly prescribed basal insulin analog [15]. The replacement in the A-chain of asparagine by glycine in position A21 imparts a shift of the isoelectric point (from a pH of 5.4 to 6.7), making it less soluble at physiological pH and prolonging its duration of action up to 24 hours, with no pronounced peak in activity. Following the injection, insulin glargine forms a subcutaneous depot, from which it is slowly absorbed. This provides a relatively uniform concentration for 24 h, which allows mimicking basal endogenous insulin secretion [16]. It has been proven that early basal insulin initiation with insulin glargine preserves beta-cell function when compared to prolonged continuation of solely oral therapy [17]. As the natural course of diabetes progresses, in-

creasing the dose and using combinations of insulins are needed to intensify treatment. Therefore, insulin glargine is suitable for a spectrum of treatment intensities allowing flexibility in regimen which adds to patient convenience. Thus, the early introduction of insulin in patients with type 2 diabetes is to be encouraged [18].

1.4. Rationale for Current Study

Insulin glargine brand "Glaritus®" has been registered in Nepal since 2015. The current trial was designed to investigate the effects of glargine-based strategy (Glaritus®) in Nepalese patients with T2DM who could not achieve adequate glycemic control with oral and/or insulin therapy. The approach of the study aimed to more accurately represent the nature of therapy adjustment in routine clinical practice in Nepal. Therefore, Glaritus® initiation and optimization was decided by the treating clinician rather than by a protocol-driven clinical trial setting. Over the last decade, insulin glargine has become a standard of care in diabetes treatment in Nepal due to its well-established safety and efficacy profiles [12]. HbA1c is an excellent composite endpoint dependent upon both post-prandial glucose (PPG) and fasting plasma glucose (FPG) levels. Since we used a "treat-to-target" design of the study, we evaluated parameters FPG and HbA1c.

2. Material and Methods

2.1. Study Design

This is a prospective, multi-centric, single arm, post marketing, observational, phase IV study to assess the safety and effectiveness of Glaritus® in Nepalese patients with T2DM.

2.2. Study Objectives

This being a post-marketing surveillance, the primary objective of the study was to evaluate the safety of Glaritus® in Nepalese patients at 3 centers from September 2015 to December 2016. The secondary objectives were to evaluate the efficacy of Glaritus® in terms of percentage of patients achieving HbA1c goal of less than 7% at the end of study and mean changes in HbA1c & FPG levels from baseline at 6 months of therapy.

2.3. Patients

52 patients were included from 3 different study sites in Nepal (Bharatpur, Kathmandu and Pokhra). All patients were enrolled after obtaining written informed consent. Local ethics committee approval was not required for post-marketing surveillance as per the Department of Drug Administration (DDA), Nepal. Relevant medical history, vital signs evaluation and thorough clinical examination were carried out before inclusion of the patient into the surveillance. The lab parameters included determination of FPG and HbA1c. Renal function tests and liver function tests were also carried out for safety as-

sessment. Follow up visits were conducted at 3 month and at 6 months of therapy when the safety and clinical assessment were repeated as per protocol requirements.

The main inclusion criteria were patients aged 18 to 65 years with T2DM diagnosed at least 1 year ago, not responding to/uncontrolled on the current therapy of oral antidiabetic medications (Insulin-naïve patients) or on insulin (basal/bolus), with HbA1c levels > 7% and ≤11%, having BMI < 40 kg/m^2, and no history of ketonemia. Patients were excluded from study if they had history of known hypersensitivity to glargine, had history of ketonemia, were pregnant or lactating females, were suffering from either hepatic or renal dysfunction, had active cardiovascular disease or had history of recurrent severe hypoglycemia.

2.4. Medication

Glaritus® cartridge to be used with My Pen insulin delivery device (manufactured by Wockhardt Limited, India) was the surveillance medication. This was a post-marketing, observational study, hence no free medication was provided to the patients. The mode of administration was subcutaneous, once daily injection and dose of administration was as per the discretion of the investigator. Oral hypoglycemic agents and other insulin were allowed as concomitant medication. The titration of dosage of Glaritus®, other insulin and oral hypoglycemic agents was determined on the basis of blood glucose levels. The total duration of study was 6 months.

2.5. Safety and Efficacy Variables

Safety assessment was done by evaluating occurrence of hypoglycemia, renal function tests and liver function tests any other adverse events reported.

The primary efficacy variable was HbA1c. Final evaluation on efficacy was based on the percent patients achieving HbA1c goal of less than 7% and mean change in HbA1c level (from baseline to final visit *i.e.*, post treatment with surveillance medication for 6 months). The secondary efficacy variable was FPG. The mean changes of FPG from baseline visit to final visit were evaluated.

2.6. Statistical Analysis

Since the study was designed as "proof-of-concept" in Nepal, sample size was not estimated using statistical tests. It was determined arbitrarily as per investigator's clinical judgment. The data was subject to descriptive statistics. Paired t-test was used to evaluate the statistical significance of differences in HbA1c and FPG values. Demographic data such as age, gender, weight, height and BMI were summarized overall and by study-sites. Occurrence of adverse events (hypoglycemia) at each assessment visit was recorded and summarized using count and percentage. Age, weight, height and BMI are summarized using statistical measures of mean and standard deviation. Gender is summarized using frequency and percentages.

3. Results

52 patients were enrolled in this study at 3 centers. Figure 1 depicts the percentage contribution of data from each site. Table 1 shows the summary statistics of demography parameters age, height, weight, BMI, gender and study-site wise distribution. The mean (range) age of patients was 52.79 years (19 - 65) and mean (range) BMI was 26.55 (16.9 - 35.5).

Table 2 shows visit-wise mean HbA1c and FPG values. The mean HbA1c values reduced from 9.16% to 7.15% at the end of study. The mean FPG value of entire group reduced from 239.94 mg/dL to 151.31 mg/dL towards the end of study.

Figure 2 shows the frequency and percentage of patients achieving HbA1c goal of less than 7% at various assessment visits.

Twenty one point zero five (21.05)% of the enrolled subjects achieved the goal of HbA1c < 7% at 3 months of therapy, whereas 52.50% achieved the goal at the end of 6 months of therapy.

Figure 3 shows the change in HbA1c values from baseline to the end of visit (Visit 3 and Visit 4).

Paired t-test was used to compare change in HbA1c values from baseline to end of visit (Visit 3 and Visit 4). The hypothesis testing was performed at 5% LOS. P value was highly significant < 0.0001.

Figure 4 shows the change in FPG values from baseline to the end of visit (Visit 3 and Visit 4).

Paired t-test was used to compare change in FPG values from baseline to end of visit (Visit 3 and Visit 4). The hypothesis testing was performed at 5% LOS. P value was highly significant < 0.0001 at the end of Visit 3 and 4.

Table 3 depicts the percentage of patients experiencing hypoglycemia. 3.85% subjects were recorded to experience hypoglycemia in Visit 3 whereas 1.92% subjects were recorded in Visit 4. No significant change in renal or liver functions occurred during the treatment.

There was no significant change in renal or liver functions during treatment in terms of serum creatinine and liver enzymes. None of the subjects experienced any other AE, thus indicating that Glaritus® was well tolerated by the study subjects.

Table 1. Baseline demographic characteristics.

Parameters	Results
Age (Mean ± SD)	52.79 ± 7.97 years
Height (Mean ± SD)	158.07 ± 8.88 cms
Weight (Mean ± SD)	65.91 ± 9.33 kg
BMI (Mean ± SD)	26.55 ± 4.16 kg/m^2
Gender	
Male	17
Female	30
Missing	5

Table 2. Visit wise mean HbA1c and FP values.

Parameter	Visit 1 (Day −7 to Day 0)	Visit 2 (at Day 1)	Visit 3 (after 3 months ± 5 days)	Visit 4 (after 6 months ± 7 days)
HbA1c—n	51	50	38	40
Mean ± SD (%)	9.16 ± 1.20	9.19 ± 1.20	7.85 ± 1.23	7.15 ± 0.94
FPG—n	50	50	50	44
Mean ± SD (mg/dL)	239.94 ± 79.59	238.70 ± 79.61	171.42 ± 64.93	151.31 ± 47.35

Table 3. Percentage of subjects experiencing hypoglycemia.

Visit (n = 52 for both visits)	No. of subjects experiencing hypoglycemia	Percentage
Visit 3 (at 3 months)	2	3.85%
Visit 4 (at 6 months)	1	1.92%

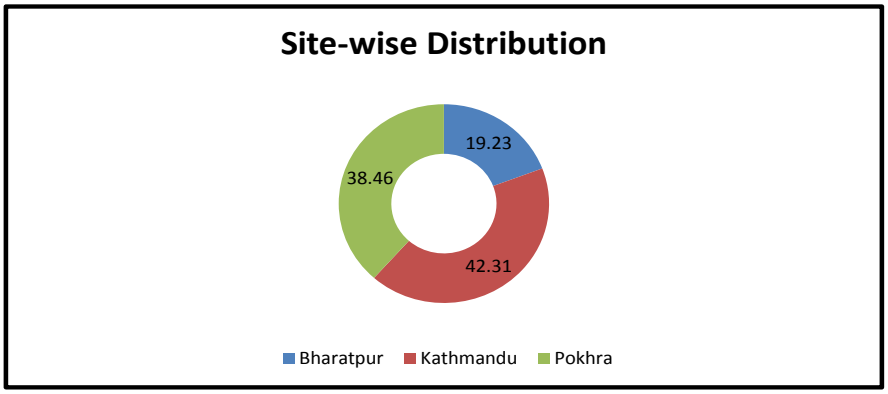

Figure 1. Percentage contribution of data from each site.

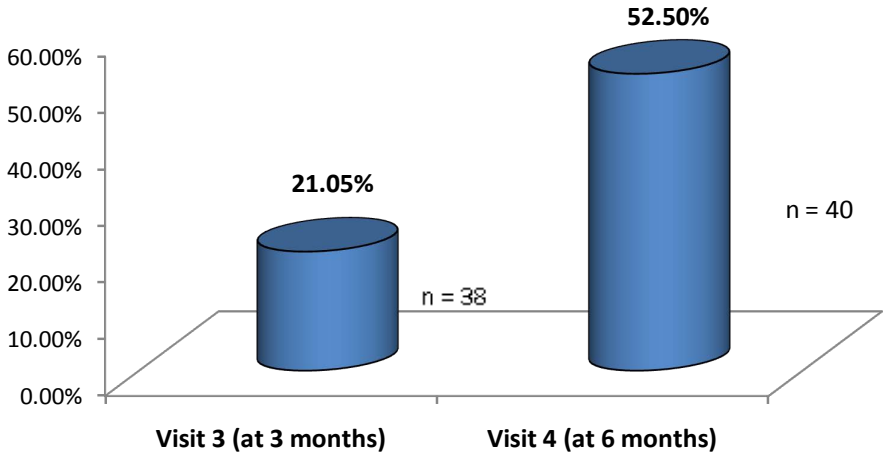

Figure 2. Percentage of patients achieving HbA1c goal of <7%.

4. Discussion

Glargine was the first-to-be-introduced once-daily, long-acting insulin analog efficacious for 24 hours. It has now been in clinical use for more than 10 years

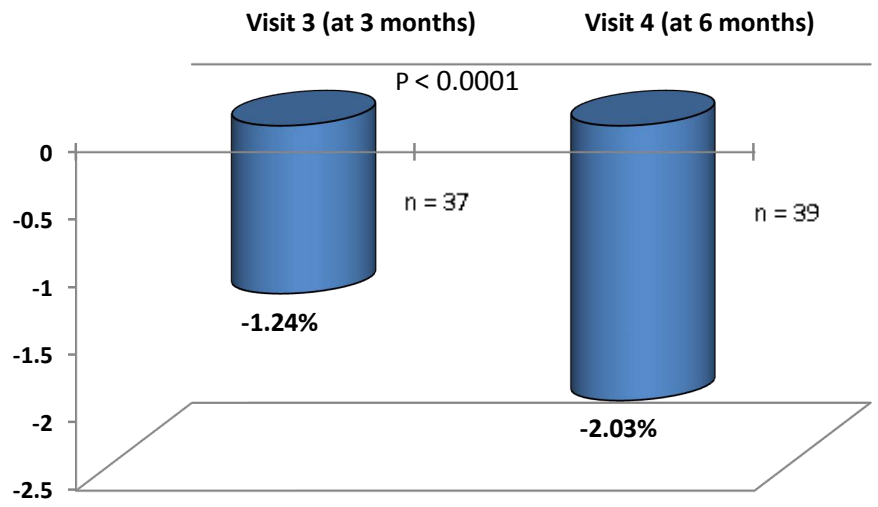

Figure 3. Mean change in HbA1c values (%) from baseline to Visit 3 and 4.

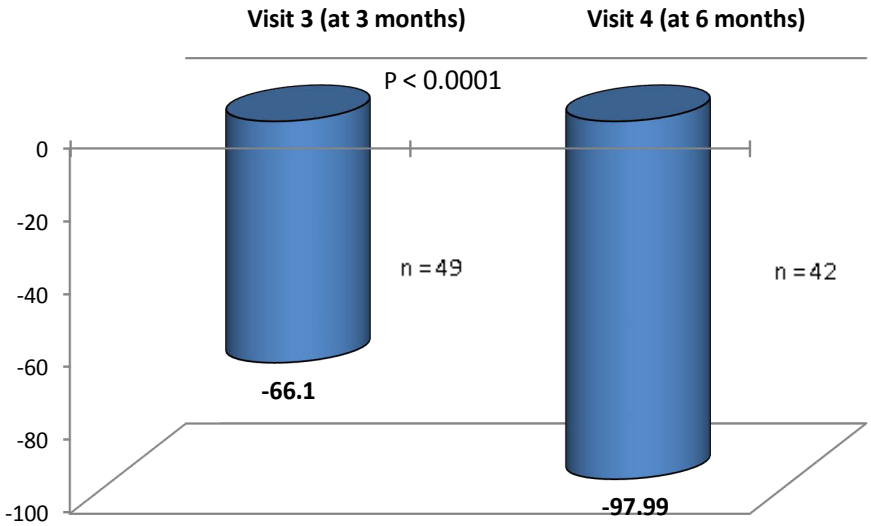

Figure 4. Mean change in FPG values (mg/dL) from baseline to Visit 3 and 4.

[19]. Insulin glargine has a delayed absorption from the subcutaneous tissue depot which leads to prolonged action, and a relatively consistent, peak-less concentration–time profile, thus reducing the risk of positive and negative glycemic excursions [20]. The safety and efficacy of insulin glargine is well established in many large randomized controlled clinical studies, and also supported by American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) recommendations. Many clinicians would agree that insulin glargine continues to achieve success in the real-world clinical setting. Our study stands testimony to its safety and efficacy in the Nepalese population. Individualizing HbA1c goals is the most appropriate approach to the effective management of diabetes. Importantly, as insulin glargine can be easily combined with other hypoglycemic agents, it has a central role in individualizing treatment.

The most common approach to initiate pharmacotherapy in T2DM is met-

formin, which can be further intensified by adding and replacing oral antidiabetic drugs of other classes or injectable GLP-1 agonists. Given the natural clinical course of T2DM, many patients will eventually require insulin, usually beginning from one injection of basal insulin preparation [12] [21] [22]. Even though, many insulin analogues have been developed so far, insulin glargine has favorable pharmacokinetic properties that allow consistent insulin activity over 24 h with only a single injection. This makes insulin glargine the most widely prescribed long acting insulin analogue [11].

In our study only 3.85% and 1.92% subjects experienced hypoglycemia at 3 months and 6 months of Glaritus® therapy, respectively. The improvement in the HbA1c values from baseline to the end of study is statistically significant at 5% LOS (p-value < 0.05). Similarly, the change in the FPG values from baseline to the end of study is statistically significant at 5% LOS (p-value < 0.05). The reduced risk of hypoglycaemia and better FPG observed with Glaritus® offers additional positive features, including greater flexibility. The flexibility in timing the insulin glargine dose, although requiring dosing at the same time each day, may provide patients with some respite from the strict insulin regimens, especially in insulin initiators.

The lower incidence of hypoglycemia can be explained by the flat time-action profile of insulin glargine with no pronounced peak, which would facilitate maintenance of euglycemia with reduced blood glucose excursions. There was no significant change in renal or liver functions during treatment. None of the subjects experienced any other AE.

Glaritus® offers both increased convenience (once-daily administration) and safety (reduced risk of hypoglycemia) when attempting to reach the target HbA1c level of 7.0%. HbA1c target was achieved in more than 52.54% of subjects, similar to other previous studies [23].

Our results are in line with previous studies conducted in other geographies. Freemantle *et al.* [24] conducted a network meta-analysis comparing the efficacy and safety of insulin glargine with other basal insulin therapies in patients with T2DM. Change in HbA1c was comparable with other insulins (detemir, NPH, premixed etc.) and incidence of hypoglycemia was significantly lower with glargine. Similarly, Pandya *et al.* [25] conducted a pooled analysis of 24-week data from nine prospective open-label, multicenter, phase 3/4, two-arm, parallel-group, randomized controlled trials, where patients with T2DM aged 18 - 80 years received insulin glargine (used as a basal insulin regimen) or comparators (including OADs, insulin lispro, insulin lispro 75/25, NPH insulin, NPH insulin 30/70, and lifestyle/dietary measures). They concluded in favor of insulin glargine, which was associated with better glycemic control and a reduced incidence of hypoglycemia versus comparator interventions in both younger and older T2DM patients. Pscherer *et al.* [26] reported the results of their study performed on 20 diabetic patients with end stage renal disease on hemodialysis treated with insulin glargine. In this nine-month study, mean HbA1c reduced by 0.9% ($p < 0.01$) and severe hypoglycemic events were not reported. In the present study,

the target HbA1c level of 7.0% or less was achieved for over half of study subjects within the short study duration. Most of the clinical practice guidelines recommend the target glucose level to prevent diabetes related vascular complications and glycemic goals of HbA1c ≤ 7.0% (53 mmol/mol) [27]. However, a new perspective was introduced by three recently published large RCT studies (ACCORD, ADVANCE, VADT). They have demonstrated no significant benefits in cardiovascular outcome with intensive glycemic control [28] in participants who had T2DM for 8 to 11.5 years. These studies depict that the glycemic target should be individualized according to age, comorbidities, duration of T2DM, presence of macro- and micro-vascular complications and propensity for hypoglycemia.

Limitations and Strengths of the Study

The limitations of the present study include its single-arm, open-label design, which could have introduced physicians' and patients' bias, however, it would have been difficult to use a double-blind design in the real-world practice. The sample size of the study was small which must be considered before interpreting the results.

Although the length of the study was fairly short in view of the chronic nature of T2D, but the duration was sufficient for treatment to reach a steady state and insulin glargine treatment optimization process to be completed. The study duration was also adequate to assess treatment effect. This study's strength is that it is the only study to our knowledge which evaluates insulin glargine-based treatment with/without OAD combination in Nepalese patients with uncontrolled type 2 diabetes.

5. Conclusion

In patients with type 2 diabetes mellitus inadequately controlled on OADs and/or insulin, initiation with Glaritus® significantly improved glycemic control with good tolerability and acceptability. The results of our study support current guidelines and add to the body of evidence supporting the use of insulin glargine, but from a Nepalese T2DM population perspective. This analysis in T2DM Nepalese patients shows that Glaritus® helps to improve glycemic control and, at the same time avoid severe and nocturnal hypoglycemia. Insulin glargine offers a safer peak-less glycemic profile, hence suited to aggressive treatment regimens. From a societal perspective, it can help more patients achieve tight glycemic control as recommended by current treatment guidelines. Further carefully designed, long-term and prospective studies are needed to evaluate the overall benefits and clinical efficacy of Glaritus® injection in Nepalese diabetic population.

Acknowledgements

Medical writing support was provided by Dr. Pratishtha Banga, MD.

Conflicts of Interest

All three investigators received research grant for undertaking the PMOS. However, none of the authors have any direct commercial interest in Glaritus®.

References

[1] IDF Diabetes Atlas 7th Edition (2015) https://www.idf.org/e-library/epidemiology-research/diabetes-atlas/13-diabetes-atlas-seventh-edition.html

[2] Misra, A. and Shrivastava, U. (2013) Obesity and Dyslipidemia in South Asians. *Nutrients*, **5**, 2708-2733. https://doi.org/10.3390/nu5072708

[3] Gyawali, B., Sharma, R., Neupane, D., Mishra, S.R., van Teijlingen, E. and Kallestrup, P. (2015) Prevalence of Type 2 Diabetes in Nepal: A Systematic Review and Meta-Analysis from 2000 to 2014. *Global Health Action*, **8**, 29088. https://doi.org/10.3402/gha.v8.29088

[4] World Bank (2013) Urban Growth and Spatial Transition: An Initial Assessment. World Bank, Washington DC.

[5] Upadhyay, D.K., Palaian, S., Ravi Shankar, P., Mishra, P. and Sah, A.K. (2007) Prescribing Pattern in Diabetic Outpatients in a Tertiary Care Teaching Hospital in Nepal. *Journal of Clinical and Diagnostic Research*, **3**, 248-255.

[6] Sapkota, R.P., Upadhyaya, T., Gurung, G., *et al.* (2018) Need to Improve Awareness and Treatment Compliance in High-Risk Patients for Diabetic Complications in Nepal. *BMJ Open Diabetes Research and Care*, **6**, e000525. https://doi.org/10.1136/bmjdrc-2018-000525

[7] Dahal, P., Maharjan, L., Dahal, B. and Gupta, K. (2015) Assessment of Prescription Patterns in Hypertensive and Diabetic Patients Visiting Private Tertiary Care Hospital of Dharan Municipality, Nepal. *Sunsari Technical College Journal*, **2**, 44-47.

[8] Holman, R.R., Paul, S.K., Bethel, M.A., Neil, H.A. and Matthews, D.R. (2008) 10-Year Follow-Up of Intensive Glucose Control in Type 2 Diabetes. *The New England Journal of Medicine*, **359**, 1577-1589. https://doi.org/10.1056/NEJMoa0806470

[9] Bergenstal, R.M., Rosenstock, J., Arakaki, R.F., Prince, M.J., Qu, Y., Sinha, V.P., *et al.* (2012) A Randomized, Controlled Study of Once-Daily LY2605541, a Novel Long-Acting Basal Insulin, versus Insulin Glargine in Basal Insulin-Treated Patients with Type 2 Diabetes. *Diabetes Care*, **35**, 2140-2147. https://doi.org/10.2337/dc12-0060

[10] Garber, A.J., King, A.B., Del Prato, S., Sreenan, S., Balci, M.K., Munoz-Torres, M., *et al.* (2012) Insulin Degludec, an Ultra-Longacting Basal Insulin, versus Insulin Glargine in Basal-Bolus Treatment with Mealtime Insulin Aspart in Type 2 Diabetes (BEGIN Basal-Bolus Type 2): A Phase 3, Randomised, Open-Label, Treat-to-Target Non-Inferiority Trial. *The Lancet*, **379**, 1498-1507. https://doi.org/10.1016/S0140-6736(12)60205-0

[11] Heller, S., Buse, J., Fisher, M., Garg, S., Marre, M., Merker, L., *et al.* (2012) Insulin Degludec, an Ultra-Long Acting Basal Insulin, versus Insulin Glargine in Basal-Bolus Treatment with Mealtime Insulin Aspart in Type 1 Diabetes (BEGIN Basal-Bolus Type 1): A Phase 3, Randomised, Open-Label, Treat-to-Target Non-Inferiority Trial. *The Lancet*, **379**, 1489-1497. https://doi.org/10.1016/S0140-6736(12)60204-9

[12] Inzucchi, S.E., Bergenstal, R.M., Buse, J.B., Diamant, M., Ferrannini, E., Nauck, M., *et al.* (2012) Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach: Position Statement of the American Diabetes Association (ADA) and the

European Association for the Study of Diabetes (EASD). *Diabetes Care*, **35**, 1364-1379. https://doi.org/10.2337/dc12-0413

[13] Ross, S.A. (2013) Breaking Down Patient and Physician Barriers to Optimize Glycemic Control in Type 2 Diabetes. *The American Journal of Medicine*, **126**, S38-S48. https://doi.org/10.1016/j.amjmed.2013.06.012

[14] Polonsky, W.H., Fisher, L., Guzman, S., Villa-Caballero, L. and Edelman, S.V. (2005) Psychological Insulin Resistance in Patients with Type 2 Diabetes: The Scope of the Problem. *Diabetes Care*, **28**, 2543-2545. https://doi.org/10.2337/diacare.28.10.2543

[15] Rotenstein, L.S., Ran, N., Shivers, J.P., Yarchoan, M. and Close, K.L. (2012) Opportunities and Challenges for Biosimilars: What's on the Horizon in the Global Insulin Market? *Clinical Diabetes*, **30**, 138-150. https://doi.org/10.2337/diaclin.30.4.138

[16] Lepore, M., Pampanelli, S., Fanelli, C., Porcellati, F., Bartocci, L., Di Vincenzo, A., *et al.* (2000) Pharmacokinetics and Pharmacodynamics of Subcutaneous Injection of Long-Acting Human Insulin Analog Glargine, NPH Insulin, and Ultralente Human Insulin and Continuous Subcutaneous Infusion of Insulin Lispro. *Diabetes*, **49**, 2142-2148. https://doi.org/10.2337/diabetes.49.12.2142

[17] Pistrosch, F., Köhler, C., Schaper, F., Landgraf, W., Forst, T. and Hanefeld, M. (2013) Effects of Insulin Glargine versus Metformin on Glycemic Variability, Microvascular and Beta-Cell Function in Early Type 2 Diabetes. *Acta Diabetologica*, **50**, 587-595. https://doi.org/10.1007/s00592-012-0451-9

[18] Owens, D.R. and Griffiths, S. (2002) Insulin Glargine (Lantus). *International Journal of Clinical Practice*, **56**, 460-466.

[19] Owens, D.R. (2011) Insulin Preparations with Prolonged Effect. *Diabetes Technology & Therapeutics*, **13**, S5-S14. https://doi.org/10.1089/dia.2011.0068

[20] Heinemann, L., Linkeschova, R., Rave, K., Hompesch, B., Sedlak, M. and Heise, T. (2000) Time-Action Profile of the Long-Acting Insulin Analog Insulin Glargine (HOE901) in Comparison with Those of NPH Insulin and Placebo. *Diabetes Care*, **23**, 644-649. https://doi.org/10.2337/diacare.23.5.644

[21] Handelsman, Y., Mechanick, J.I., Blonde, L., Grunberger, G., Bloomgarden, Z.T., Bray, G.A., *et al.* (2011) American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan. *Endocrine Practice*, **17**, 1-53. https://doi.org/10.4158/EP.17.S2.1

[22] Saisho, Y., Kou, K., Tanaka, K., Abe, T., Kurosawa, H., Shimada, A., *et al.* (2013) Postprandial Serum C-Peptide to Plasma Glucose Ratio Predicts Future Insulin Therapy in Japanese Patients with Type 2 Diabetes. *Acta Diabetologica*, **50**, 987-988. https://doi.org/10.1007/s00592-012-0441-y

[23] Riddle, M.C., Rosenstock, J. and Gerich, J., Insulin Glargine 4002 Study Investigators (2003) The Treat-to-Target Trial: Randomized Addition of Glargine or Human NPH Insulin to Oral Therapy of Type 2 Diabetic Patients. *Diabetes Care*, **26**, 3080-3086. https://doi.org/10.2337/diacare.26.11.3080

[24] Freemantle, N., Chou, E., Frois, C., Zhuo, D., Lehmacher, W., Vlajnic, A., *et al.* (2016) Safety and Efficacy of Insulin Glargine 300 u/mL Compared with Other Basal Insulin Therapies in Patients with Type 2 Diabetes Mellitus: A Network Meta-Analysis. *BMJ Open*, **6**, e009421. https://doi.org/10.1136/bmjopen-2015-009421

[25] Pandya, N., DiGenio, A., Gao, L. and Patel, M. (2013) Efficacy and Safety of Insulin Glargine Compared to Other Interventions in Younger and Older Adults: A Pooled Analysis of Nine Open-Label, Randomized Controlled Trials in Patients with Type 2 Diabetes. *Drugs Aging*, **30**, 429-438. https://doi.org/10.1007/s40266-013-0069-9

[26] Pscherer, S., Schreyer-Zell, G. and Gottsmann, M. (2002) Experience with Insulin Glargine in Patients with End-Stage Renal Disease. *Diabetes*, **216**, A53.

[27] Ko, S.H., Kim, S.R., Kim, D.J., Oh, S.J., Lee, H.J., Shim, K.H., *et al.* (2011) Committee of Clinical Practice Guidelines, Korean Diabetes Association. 2011 Clinical Practice Guidelines for Type 2 Diabetes in Korea. *Diabetes & Metabolism Journal*, **35**, 431-436. https://doi.org/10.4093/dmj.2011.35.5.431

[28] Skyler, J.S., Bergenstal, R., Bonow, R.O., Buse, J., Deedwania, P., Gale, E.A., *et al.* (2009) Intensive Glycemic Control and the Prevention of Cardiovascular Events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials: A Position Statement of the American Diabetes Association and a Scientific Statement of the American College of Cardiology Foundation and the American Heart Association. *Diabetes Care*, **32**, 187-192. https://doi.org/10.2337/dc08-9026