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Original Research Article

A Comparative Pharmacovigilance Analytical Research Study on the Glycaemic Stabilisation Rate and Safety Levels, Between Metformin Monotherapy and Combination Therapies, Among Type II Diabetic Patients

Moumita Hazra

Associate Professor, Head of Department In Charge, Department of Pharmacology, Mamata Medical College and Hospitals, Telangana, India

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Corresponding author: Dr. Moumita Hazra
Conflict of interest: Nil

Abstract

Background: Metformin causes sufficiently higher efficacious and safe glycaemic stabilisation rates, more significantly as a combination therapy than while being prescribed as a monotherapy, during the routine treatment of type-II anti-diabetic patients, in regular tertiary healthcare, due to its synergistic action with the other anti-diabetic drugs. Analysing metformin monotherapy and combination therapies based on rational pharmacotherapeutics, it might be stated that the beneficial pharmacotherapeutic effects of metformin were greater than the metformin induced adverse drug reactions.

Aim and Objectives: This comparative analytical research study was performed, to comprehend the comparative patterns of glycaemic stabilisation and pharmacovigilance between regular anti-diabetic mono- and combination treatment regimens prescribed to type II diabetic patients.

Materials and Methods: 42 type II diabetes mellitus patients, were prescribed oral metformin 250-500 mg once daily, depending upon the monotherapeutic or combination therapeutic regimen, severity or grade of type – II diabetes, the status of glycaemic stabilisation, prognostic progress of the anti-diabetic treatment, any occurrence of adverse effect, or the therapeutic control of co-morbid conditions. The percentage of during anti-diabetic treatment and post-treatment glycaemic stabilisation of the patients with metformin monotherapy and metformin combination therapies were comparatively analysed. The corresponding drug safety levels were comparatively analysed with percentage derivations.

Results: The glycaemic stabilisation rate was 100% with both metformin monotherapy as well as combination therapies. The comparative safety levels of metformin monotherapy and combination therapies, deduced with percentages, showed 100% safety levels.

Conclusion: Glycaemic stabilisation was found among all patients undergoing metformin monotherapy and metformin combination therapy, and both the types of metformin treatments have high safety levels.

Keywords: Comparative Pharmacovigilance, Glycaemic Stabilisation Rate, Drug Safety Levels, Metformin Monotherapy, Metformin Combination Therapies, Anti-Diabetic Treatment.

Introduction

Metformin, the most commonly prescribed biguanide, causes gradual overwhelming of insulin resistance as well as hypoglycaemia, by activating the enzyme 5' adenosine monophosphate, which catalyses the activation of protein kinase. Metformin also stabilises HbA1c levels, along with resulting in weight reduction, among the patients affected with diabetes associated obesity. Metformin possesses pleotropic effects on glucose metabolism. Metformin inhibits hepatic gluconeogenesis in a substrate selective manner, through the transcription, allosteric, substrate availability, or redox mechanisms; and by metformin inhibition of complex I, leading to reductions in hepatocellular energy charge and other downstream events (e.g., adenosine monophosphate-activated protein kinase [AMPK] activation, fructose 1, 6-bisphosphatase inhibition, inhibition of glucagon signaling). Metformin alters the cellular redox balance, and the increased cytosolic redox state, due to the inhibition of glycerol-3-phosphate dehydrogenase by metformin. This is observed at clinically relevant concentrations and is the only proposed mechanism of action that predicts substrate selective (glycerol and lactate) inhibition of hepatic gluconeogenesis. Metformin causes sufficiently higher efficacious and safe glycaemic stabilisation rates, more significantly as a combination therapy than while being prescribed as a mono-therapy, during the routine treatment of type-II anti-diabetic patients, in regular tertiary healthcare, due to its synergistic action with the other anti-diabetic drugs. While furthering the rational pharmacotherapeutic significance, metformin also has an easy availability and quite convenient route of drug administration, with specific appropriateness for the initial and maintenance pharmacotherapy of different types of diabetic type II patients. This comparative analytical research study was performed, to comprehend the comparative patterns of pharmacovigilance and glycaemic stabilisation between regular anti-diabetic mono- and combination treatment regimens prescribed to type II diabetic patients. This analysis also intends to have an effect on the improvisation of future anti-diabetic therapeutic modalities as well as research innovations involving anti-diabetic patient healthcare with oral hypoglycaemic drugs.

Objective:

The objective of this pharmacovigilance analytical research study was to comparatively analyse the glycaemic stabilisation rate and the safety levels, with quantitative interpretations, between metformin monotherapy and combination therapies, among type II diabetic patients.

Materials and Methods:

Ethical Approval:

At first, the Institutional Ethics Committee clearance and approval was taken for conducting this study. The study was conducted in accordance with the ethical principles of Declaration of Helsinki and Good Clinical Practices contained within the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH-E6 and ICH-E17), and in compliance with the global regulatory requirements. An informed consent was obtained from each patient.

Selection Criteria of the Study Participants:

Inclusion criteria:

The inclusion criteria were as follows: (i) patients of any gender, (ii) patients within 35 and 60 years, (iii) patients of around 60 kg average body weight, (iv) patients presenting with type II diabetes mellitus, (v) type II diabetes mellitus American Diabetes Association diagnosis criteria, (vi) cooperative and conscious patients, (vii) patients willing to

undergo all pre- and post-treatment investigations and willing to complete the entire course of treatment, (viii) patients who have given consent and are willing to go for a follow-up, (ix) patients not taking any previous antidiabetic drug, and (x) patients not taking any concomitant medication.

Exclusion criteria:

The exclusion criteria were as follows: (i) uncooperative or unconscious patients, (ii) patients below 35 and above 60 years, (iii) patients presenting with any disease, other than type II diabetes mellitus, (iv) patients with a history of hypersensitivity to any of the study drugs, (v) patients with high-risk diseases or comorbidities, (vi) cardiac, renal, or any other associated complications or comorbidities, (vii) any chronic disease intervening with the study data, (x) pregnant or lactating women, (xi) paediatric or geriatric patients, (xii) other associated medical illness or disorders, like urogenital tract infections, having impact on study results, and (xiii) female patients using hormonal contraceptives.

Study design:

This was a global, multi-centre, prospective, open-labelled study.

Study population:

The study population was 42 type II diabetes mellitus patients, in tertiary care hospitals.

Place of study:

The place of research study and the compilation of the study literature were the Departments of Pharmacology, Clinical Pharmacology, Molecular Pharmacology, Endocrinology, Diabetology and Metabolic Medicine, Pharmacovigilance, Rational Pharmacotherapeutics, Evidence Based Medicine, Clinical Medicine, Clinical Pathology and Pathology, in Mamata Medical College and Hospitals, Rama Medical College Hospital and Research Centre, Rama University, Dr. Moumita Hazra's Polyclinic and Diagnostic Centre, Hazra Nursing Home, and Hazra Polyclinic And Diagnostic Centre.

Study period:

The study period, including the research study and the compilation of the study literature, was 1 year, that is, from February, 2021 to April, 2022.

Study Procedure:

42 type II diabetes mellitus patients, were prescribed oral metformin 250-500 mg once daily, depending upon the monotherapeutic or combination therapeutic regimen, severity or grade of type – II diabetes, the status of glycaemic stabilisation, prognostic progress of the anti-diabetic treatment, any occurrence of adverse effect, or the therapeutic control of co-morbid conditions. Among the 42 patients receiving metformin, the diabetic patients whose glycaemic condition were uncontrolled with metformin, that is, (i) who had achieved adequate glycaemic control with metformin monotherapy, or (ii) who were lost to follow-up, or (iii) who had dropped out due to adverse effects, or (iv) who had withdrawn voluntarily, were prescribed the combination therapy of metformin and other anti-diabetic drugs. Some patients were also prescribed the combination therapeutic regimen, from their initial consultation visit onwards.

The patients' characteristics, diabetic symptoms assessment, patients' disease and disease-related history were recorded with a proforma. Then, thorough general physical examination and systemic examination were performed on the patients under study. The relevant blood, urine and other investigations were done to confirm the progressing health status of the patients being treated.

The efficacy assessment was done, by recording the fasting and the post-prandial blood sugar level, HbA1c level and urine routine examination findings including sugar and albumin levels and microscopy, at baseline level, and after administering metformin monotherapy or combination therapy, at every

1 month interval, and at further follow-up once every month.

The rate of during anti-diabetic treatment and post-treatment glycaemic stabilisation of the patients were recorded at every month and at the monthly follow-up visits, with metformin monotherapy and metformin combination therapies, and the recordings were comparatively analysed. Then, these findings were quantitatively analysed with percentage derivations.

The safety assessment was done by the monitoring of the occurrence of any adverse drug reaction, like hypoglycaemia, weakness, gastrointestinal disturbances, abdominal pain, and upper respiratory tract infections, after metformin monotherapy or combination therapies, at the baseline level, at every 1 month interval, and at further follow-ups once every month, with Adverse Reactions Case Report Form. Then these drug safety recordings of the patients on metformin monotherapy or combination therapies were comparatively analysed with percentage derivations, to deduce the corresponding drug safety levels.

The anti-diabetic medical healthcare patient satisfaction was also evaluated by the response of the patients to the different attributes, like immediate treatment delivery, appropriate and convenient investigations and treatment, quickly controlled diabetes, safe and tolerable treatment, easily accessible medications, convenient administration of medications, and maintenance of symptom-free controlled diabetic period.

Statistical Analysis:

The research findings recorded in this study, were statistically analysed by Test of significance with p values, and various percentages, with subsequent graphical illustrative representations.

Results:

The demographic characteristics of the patients were comparable. From among 42 type II diabetes mellitus patients, receiving metformin monotherapy, the uncontrolled diabetic patients, (i) who had achieved adequate glycaemic control with metformin monotherapy, or (ii) who were lost to follow-up, or (iii) who had dropped out due to adverse effects, or (iv) who had withdrawn voluntarily, were prescribed metformin combination therapies. There was significant decrease in the blood sugar levels and the HbA1c levels, among type II diabetic patients, on metformin monotherapy and combination therapies, at baseline level, and after administering metformin monotherapy or combination therapy, at every 1 month interval, and at further follow-up once every month. The glycaemic stabilisation rate was 100% with both metformin monotherapy as well as combination therapies, as depicted in Figure 1.

Table 1: Comparative Pharmacovigilance Assessment Between Metformin Monotherapy and Combination Therapies

Table 1 a:

ADVERSE DRUG REACTIONS WITH METFORMIN MONOTHERAPY	PATIENT NUMBER OF OCCURRENCE OF ADVERSE DRUG REACTIONS n (%)	p-VALUE
hypoglycaemia	0 (0%)	Nothing significant
weakness	1 (0%)	Nothing significant
gastrointestinal disturbances	0 (0%)	Nothing significant
abdominal pain	0 (0%)	Nothing significant
upper respiratory tract infections	0 (0%)	Nothing significant

Table 1 b:

ADVERSE DRUG REACTIONS WITH METFORMIN COMBINATION THERAPIES	PATIENT NUMBER OF OCCURRENCE OF ADVERSE DRUG REACTIONS n (%)	p-VALUE
hypoglycaemia	0 (%)	Nothing significant
weakness	0 (%)	Nothing significant
gastrointestinal disturbances	0 (%)	Nothing significant
abdominal pain	0 (%)	Nothing significant
upper respiratory tract infections	0 (%)	Nothing significant

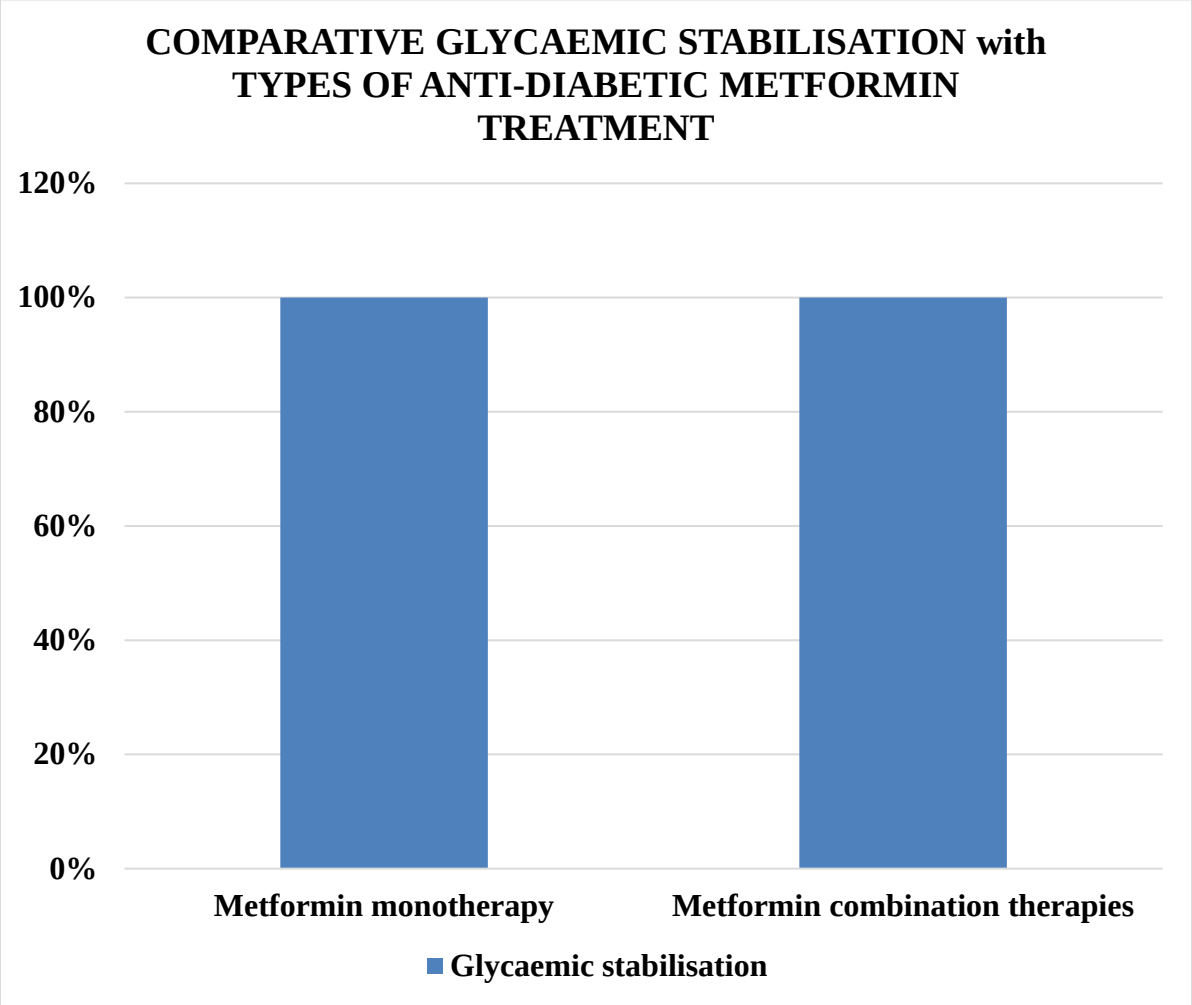

Figure 1: Comparative Glycaemic Stabilisation with Types of Anti-Diabetic Metformin Treatment

With the metformin monotherapy, one patient has manifested the adverse effect of occasional weakness, but there were no adverse drug reactions found with metformin combination therapies. Thus, the adverse drug reactions with metformin monotherapy and combination therapies were statistically non-significant, as depicted in Table 1.

The monotherapy of metformin and the combination therapies of metformin were observed to be safe, at baseline level, and after administering metformin monotherapy or

combination therapy, at every 1 month interval, and at the further follow-ups, once every month. The monotherapy as well as the combination therapies of metformin were safe and tolerable. These study findings were recorded, thoroughly analysed and quantitatively interpreted. Then, the comparative safety levels of metformin monotherapy and combination therapies, were deduced with percentages, which showed 100% safety levels with the prescription of both metformin monotherapy and combination therapies, as depicted in Figure 2.

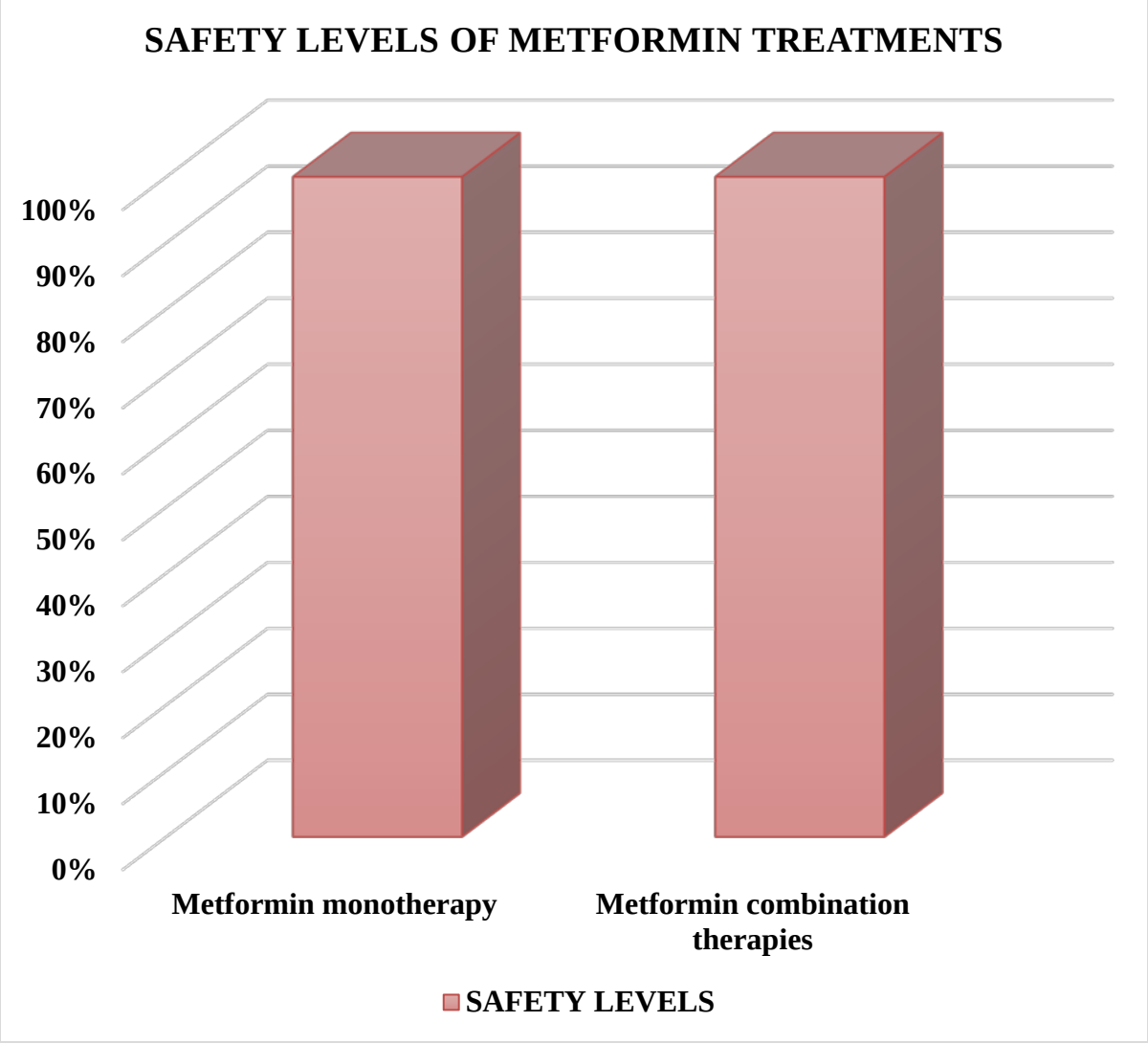

Figure 2: Comparative Safety Levels of Metformin Monotherapy and Combination Therapies

The patient response to the various attributes of anti-diabetic medical healthcare, like immediate treatment delivery, appropriate and convenient investigations and treatment, quickly controlled diabetes, safe and tolerable treatment, easily accessible medications, convenient administration of medications, and maintenance of symptom-free controlled diabetic period, showed that all the patients were satisfied with the anti-diabetic medical healthcare, as depicted in Table 2.

Table 2: Anti-Diabetic Tertiary Medical Healthcare Patient Satisfaction

Healthcare attributes	Patients' response: Satisfied	Patients' response: indeterminate	Patients' response: Unsatisfied
Immediate treatment delivery	Satisfied	-	-
Appropriate and convenient investigations and treatment	Satisfied	-	-
Quickly controlled diabetes	Satisfied	-	-
Safe and tolerable treatment	Satisfied	-	-
Easily accessible medications	Satisfied	-	-
Convenient administration of medications	Satisfied	-	-
Maintenance of symptom-free controlled diabetic period	Satisfied	-	-

Discussion:

From this comparative analytical research study, it was derived that the demographic characteristics of the patients were comparable. Among 42 type II diabetes mellitus patients, receiving metformin monotherapy, or combination therapies, there was significant decrease in the blood sugar levels and the HbA1c levels, at baseline level, and after administering metformin monotherapy or combination therapy, at every 1 month interval, and at further follow-ups, once every month. The glycaemic stabilisation rate was 100% with both metformin monotherapy as well as combination therapies.

With the metformin monotherapy, one patient had manifested the adverse effect of occasional weakness, but there were no adverse drug reactions found with metformin combination therapies. Thus, the adverse drug reactions with metformin monotherapy and combination therapies were statistically non-significant. The monotherapy of metformin and the combination therapies of metformin were observed to be safe, at baseline level, and after administering metformin monotherapy or combination therapy, at every 1 month interval, and at further follow-up once every month. Therefore, the monotherapy as well as the combination therapies of metformin were safe and tolerable. The comparative safety levels of metformin monotherapy and combination therapies, deduced with percentages, showed 100% safety levels.

The patient response to the various attributes of anti-diabetic medical healthcare, like immediate treatment delivery, appropriate and convenient investigations and treatment, quickly controlled diabetes, safe and tolerable treatment, easily accessible medications, convenient administration of medications, and maintenance of symptom-free controlled diabetic period, showed that all the patients were satisfied with the anti-diabetic medical healthcare.

Analysing metformin monotherapy and combination therapies based on rational pharmacotherapeutics, it might be stated that the beneficial pharmacotherapeutic effects of metformin were greater than the metformin induced adverse drug reactions.

In certain studies, it was demonstrated that metformin was associated with a lower or no significant difference in HbA1c levels compared with any other anti-diabetic drug. Some studies have demonstrated that the early treatment with metformin is associated with reduced cardiovascular morbidity and total mortality in newly diagnosed type 2 diabetic patients. In a study, it was deduced that after a

median period of 10 years, patients experienced a 39% risk reduction for myocardial infarction and a 36% reduction for total mortality, compared with conventional diet treatment. Similar benefits were not observed in those randomly assigned to sulfonylurea or insulin. Metformin is more advantageous than insulin and some types of insulin secretagogues, in the fact that by decreasing excess hepatic gluconeogenesis without raising insulin levels, metformin causes significant hypoglycaemia when used as a monotherapy. Due to this pharmacological function, metformin is widely considered an ideal first-line agent for the treatment of type II diabetes, as recommended by several clinical guidelines. Metformin also reduces the risk of developing diabetes in individuals who are at high risk for the disease. So, metformin has been considered to have a significant role in diabetes prevention.

In one study, it was reported that the gastrointestinal adverse effects of metformin were reduced, when metformin capsules were administered instead of metformin tablets, as the preferred drug formulations. In few studies, it was observed that gastrointestinal side effects could be overcome by the administration of metformin tablets, with meals; with careful dose adjustment; or the administration of an extended-release form of metformin. In one study, it was found that pernicious anaemia occurred by vitamin B_{12} deficiency, due to prolonged and continuous metformin intake. Metformin has shown to reduce weight. In several studies, metformin has caused different other adverse effects, like pancreatitis, hepatitis, vitamin B_{12}, coagulation abnormalities, and reactive hypoglycaemia. In another study, few patients had manifested lactic acidosis[1-9].

Conclusion:

Therefore, on comparative analytical research, it was concluded that the glycaemic stabilisation rate was found to be 100% with both metformin monotherapy as well as combination therapies; and the comparative safety levels of metformin monotherapy and combination therapies, deduced with percentages, showed 100% safety levels. These conclusions demarcated that metformin is very effective in causing adequate glycaemic stabilisation and higher safety levels, in the routine pharmacotherapeutic type II anti-diabetic treatment.

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Declarations:

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