Review Article

A Systematic Review of Oralsemaglutide for Type II Diabetes

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ABSTRACT

Type 2 Diabetes mellitus is defined as metabolic disorder, for which the prevalence is getting very high close to a pandemic. Nearly more than three by fourth of the global population have type 2 Diabetes, making gestational diabetes and type 1 Diabetes (10%) with less incidence having symptoms like polydipsia, etc. It is diagnosed by Random, Post Prandial and Glycosylated Hemoglobin test. There are several class of medications like Alpha-Glycosidase Inhibitors, Biguanides & GLP-1 receptor agonists. Semaglutide is an agonist of glucagon-like-peptide 1 receptor. Formulation of Semaglutide into subcutaneous injection was successfully performed in the year of 2017 by Novo Nordisk, which was gloriously approved by the regulatory agencies. After two years from this incident, this drug was formulated and marketed in the form of tablet under the brand name "Rybellus". Semaglutide can also be considered as drug used in treatment of cardiovascular ailments like atherosclerosis other than anti-diabetic effect. Out of the oral GLP-1 agonizing agents, Semaglutide emerges to be one of the best drugs with anti-diabetic activity. The safety profile of oral Semaglutide is also looking greater in comparison with other members of the same class.

Keywords: Semaglutide, diabetes, pioneer, type ii diabetes, glp 1 receptor, blood glucose.

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INTRODUCTION

There are several chronic metabolic disorders in the world, whose prevalence is higher when compared to the most diseases and even disorders. Out of this chronic metabolic disorders, type 2 Diabetes mellitus is one such metabolic disorder, for which the prevalence is getting very high close to a pandemic. Based on the number of patients getting diagnosed with diabetes, it can be stated that the affected population with the diabetes can become twice the current population by the next 10 years.

Even if there is diagnostic techniques and screening methods with good sensitivity and precision, there is still no medication to eradicate Diabetes mellitus type II completely. Currently, there are several guidelines for screening methods of diabetes provided by several government regulatory bodies like diabetes association of America (ADA), WHO, etc. Medical research has established several treatment methods for diabetes mellitus. This can be based on modulation in lifestyle, effective treatment of comorbidities in diabetic patients like preparing a treatment regimen for hyperlipidemia, obesity, hypertension, etc.

Currently there are several medications for maintenance of homeostasis in metabolism related to glucose like biguanides, Alpha glucosidase inhibitors, sulphonyl urea and many more. Out of this broad spectrum of medications, physician is currently prescribing hypoglycemic agents like metformin, glimepiride, etc. Latest medications for treatment of diabetes include drugs in the class of glucagon-like peptide 1 analogues, medications based on reduction of glucagon levels. Recently, there is novel approach for administration of insulin hormone by inhalation, which has entered the market from 2006. But, this novel approach was later withdrawn due to poor aid.

Pathophysiology & Etiology [1-4]

Nearly more than three by fourth of the global population have type 2 Diabetes, making gestational diabetes and type 1 Diabetes (10%) with less incidence. The insulin in type-1 Diabetes is extraordinarily low which results in a surge of blood glucose level. This condition occurs due to an autoimmune developed loss of proper functioning of beta cells in pancreas. Some studies point out that persons with obesity are more likely to get Diabetes mellitus type 2, since this is the pattern followed by this disorder from late 20th century. About 39.1 crores people where diagnosed with Diabetes mellitus as of 2015.

There are several type of diagnostic techniques developed for diabetes like Hba1c, fasting glucose, and postprandial glucose (PP).

If diabetes cannot be controlled by lifestyle changes, the patient it may require adequate medication and insulin injection based on the severity. If blood sugar levels are

not adequately lowered, the medications like metformin are typically recommended. Many people may eventually also require insulin injections. In those on insulin, routinely checking blood sugar levels is advised. Additional treatment and surgeries can be employed for removal or maintenance of comorbidities. For example, obese persons can undergo bariatric surgery to control diabetes indirectly.

This metabolic disorder usually occurs in age group above 40 years, but in recent years due to sedentary lifestyle, even youngsters at the age of 20 are diagnosed with this.

Symptoms of Type-II Diabetes [5]

Hyperosmolar syndrome is defined as the medical condition which occurs as a result of very high blood glucose levels. The important symptom for this syndrome is rapid dehydration, which can increase the mortality rate. This syndrome is also considered to be the earliest possible sign for recognising a diabetic patient. As type II diabetes progresses, it leads to further symptoms like fatigue, delusion followed by comatosing the patient.

About 8 million people who have it don't know it. Symptoms include

1. Being very thirsty(POLYDIPSIA)
2. Enhanced frequency of urination(POLYURIA)
3. Blurry vision
4. Numbness (or) tingling sensation in all limbs
5. Fatigue/feeling worn out
6. Poor healing capacity
7. Recurrent infections
8. Feeling of hunger (POLYPHAGIA)

Atherosclerosis [6]

The medical condition in which the arteries are characterized by clogging due to leopard content in the internal walls is called atherosclerosis**.** Type II diabetes increases with atherosclerosis-related inflammation, Diabetic patients are twice as likely to have a heart attack or stroke. Past work has shown that elevated serum glucose has 2 effects on cells lining blood vessels as part of atherosclerosis.

Nephropathy [7]

Diabetic nephropathy is a common complication of type I and type II diabetes. The most common complication in diabetes respective of its type is diabetic neuropathy. In case of poor treatment against diabetes, the nephrons get clogged with clusters of blood. This in turn causes sharp reduction in glomerular filtration rate (GFR) indirectly giving way to hypertension. If the patient diagnosed with diabetes has a history of hypertension, this complication has higher incidence when compared to normal diabetic patients.

CAUSES [8]

Genetics

Scientists have found different bits of DNA that affect how your body makes insulin.

Obesity

Some scientific data suggest that resistance to insulin by ourselves takes place if the person do not have optimal Body Mass Index (BMI).

Bio-chemical factors

Imbalance in lipid profile, blood pressure and other metabolic disorders can have an impact in causing incidence of Diabetes mellitus.

Excessive glucose secretion

Persons with hepatic impairment can have higher probability of developing type 2 Diabetes mellitus (DM). This may be due to the crucial role of liver in controlling the blood glucose level.

Type-II Diabetes Risk Factors [9]

Disease/ disorder oriented

i.Family history of diabetes

ii.Middle age (45 years or above)

iii.This is usually irrespective of the ethnicity of a person.

iv.Presence of Pre diabetic stage,

v.hypertension (masked or conventional), hyperlipidemia

vi.Polycystic ovarian syndrome

vii.Frequent episodes of depression

Lifestyle oriented

Other things that raise your risk of diabetes have to do with your daily habits and lifestyle. These are the ones you can do something about:

1. Getting little or no exercise
2. Smoking
3. Stress
4. Irregular sleep cycles

Illustration and Diagnosis For Type-II Diabetes [10]

Glycosylated Hemoglobin test

Glycylated hemoglobin test is usually considered to be the most desirable test for diagnosis of TYPE-II diabetes. This blood test indicates your average blood sugar level for the past 80-120 days. If the A1C test isn't available, or if you have certain conditions that interfere with HbA1C test, your doctor may use the following test to diagnosis of Diabetes:

Random blood sugar test

Milligram of glucose (mg/dL) per decilitre of blood is

considered to be the ideal unit for this test. It can also be measured in terms of millimoles of glucose present in 1 litre of Blood (mmol/L).Since this test is independent of meal intake, 200 mg/dl is considered to be diabetic. Presence of more than three symptoms with this given reference value concludes that the person has Diabetes.

Fasting blood sugar test

After an overnight fast of about 8 hours, blood serum sample is taken.

Oral glucose tolerance test

This test is less significant in normal persons but may be generally considered during the stage of pregnancy. Overnight fasting is compulsory for this type of test. In morning the particular person is subjected to gulping down specific volume of sugary liquid just before drawing the blood sample. After 2 hours, another letter sample is taken and the rate of decrease in blood glucose level is determined.

The ranges of different tests can be summarized as follows:

Type of test	Normal	Pre-diabetes	Diabetes
Fasting glucose test	Less than 100 mg/dl	100-125 mg/dl	126 mg/dl or higher
Random (anytime) glucose test	Less than 140 mg/dl	140-199 mg/dl	200 mg/dl or higher
A1ctest	Less than 5.7%	5.7 -6.4%	6.5% or higher

Medication for Type-II Diabetes [11, 12]

In case of failure of lifestyle modifications on diabetic control, medication can be provided for treatment of diabetes. It has 2 main approaches, namely:

i.Increasing the levels of insulin-by-insulin therapy

ii.Making the human cells more responsive to insulin and probably less responsive to glucagon.

Glucagon-likepeptide-1receptor agonists(GLP-1 receptor agonists)

This class of medication is also called in Britain mimicking agents since it closely resembles the incretin hormone. The drugs of this class are highly helpful in in the growth and development of B-lymphocytes. Loss of appetite is considered to be the drawback of this medication. This mechanism is achieved by reducing the gastric emptying rate of a person. This class of drugs is highly essential in diabetic patients with comorbidities including chronic renal failure (CRF), cardiovascular problems like atherosclerosis, etc. Certain leading medical associations like American diabetic association highly recommended face this kind of drugs for diabetic patients with the above comorbidities.

This class of medication includes drugs like Semaglutide, Dulaglutide and Exenatide.

Dopamine agonist

Even though, this group of drugs helps in in reduction of resistance to insulin by the cells, the exact mechanism of action by which it interacts in our human body is still unknown. As a result, it is known to affect specific rhythm or act in a systematic manner. E.g: Bromocriptine.

Dipeptidylpeptidase-4 (DPP-4) inhibitors

These drugs are usually insulinomimetic in nature, since, it plays key role in secretion of insulin hormone by the Islets of Langerhans in pancreas. It performs this end result by inhibiting the enzyme called dipeptidylpeptidase-4. As a result, the durability of insulin is better. Since, this class of medication is linked only with insulin secretion, it plays essential role bye reduction of blood glucose level without causing hypoglycemia. For example, Linagliptin, Alogliptin, Sitagliptin, etc.

Meglitinides

This kind of medication has a mechanism of action which is closely related to DPP-4 inhibitors. But this medication is not recommended for everyone and can be toxic at times. For example, Repaglitide and Nateglinide

Thiazolidinediones

TZD helps in reduction of blood glucose level in human body by making the adipocytes and other fat cells efficiently utilise insulin. Thiazolidinediones however have some drawbacks like cardiac problems like coronary artery disease. So, this pharmacological class of medication is provided by the only after evaluating the performance and wellness of our heart. For example, Pioglitazone & Rosiglitazone are some of the widely used medications of this pharmacological classification.

Biguanides

Biguanides play a vital role in lessening the amount of glucose secreted by liver in our body. It decreases the gastric & intestinal absorption of glucose by enhancing the absorption of glucose by myocytes. Metformin (Glucophage, Metformin HydrochlorideER, Glumetza, Riomet, Fortamet) is considered to be the most widely prescribed by the for diabetes treatment. Metformin can also be combined with other drugs for type-II diabetes. It's an ingredient in the medications like canagliflozin, empagliflozin, dapagliflozin, etc.

Alpha-Glycosidase Inhibitors

This kind of medications helps in breaking down the larger polysaccharide molecules into smaller glucose particles by effectively binding and inhibiting alpha-glucosidase enzyme. These drugs are usually administered prior meals. E.g: Miglitol, Voglibose and Acarbose

Sodium-glucose transporter (SGLT)II inhibitors

Sodium glucose transporter (SGLT) II inhibitors act by extraordinarily preventing the kidneys from holding onto glucose. This is done by increasing the pore size of the nephrons. Mechanisms like tubular reabsorption & glomerular filtration is inhibited to a specific extent. This classification of drugs prescribed for patients with cardiovascular and renal ailments by diabetes association situated in United States. For example, Dapagliflozin, Empagliflozin, Canagliflozin, etc.

Sulfonylureas

Sulphonylureas are considered to be the earliest drugs which are applied for anti-diabetic treatment. This help in beta cell stimulation in pancreas. Subsequently, insulin is secreted in the islets of langerhans in larger quantities. Glimepiride, Glipizide and Gliclazide are considered to be some of the examples of this class of medication.

Semaglutide as an Anti-Diabetic[13-17]

Chronic metabolic disorder, Diabetes mellitus [DM] is one of the Diabetes mellitus [DM], which is characterized by hyperglycemia, is present in almost every developing and developed country in the world. Currently, diabetes receive separate lion's share in complete medical budget of each country. Administration of insulin and sulphonyl ureas like metformin is considered to be the primary line of treatment. But, clinical data point out that this treatment regimen can cause weight gain in patients. An ideal treatment regimen for diabetes must not cause any extremities in blood sugar levels like hyperglycemia and hypoglycemia. In case of highly effective drugs, episodes of hypoglycemia tend to occur frequently. So, this infers that the treatment regimen including sulphonyl urea areas and insulin therapy is not ideal.

In order to promote the quality of life and comfort of patients with better therapeutic efficacy, newer class of medication like glucagon-likepeptide1(GLP-1) receptor agonists (GLP-1RA) &dipeptidyl peptidase-4(DPP-4)inhibitors are administered. This modern approach does not only depend upon the modulation of insulin secretion. Decreasing gastric emptying and preventing the pathway of gluconeogenesis &glycogenolysis are some of the mechanisms by which this approach takes place. The most recent GLP-1 agonist approved by US FDA is Semaglutide.

Formulation of Semaglutide into subcutaneous injection was successfully performed in the year of 2017 by Novo Nordisk, which was gloriously approved by the regulatory agencies. After two years from this incident, this drug was formulated and marketed in the form of tablet under the brand name "Rybellus".

Mechanism of Action

An assay employing BHK cells, which express the human receptor, reported that Semaglutide is an agonist of glucagon-like-peptide 1 receptor. Blood Glucose levels in the db/db mouse model of type II diabetes was reduced by Semaglutide. Further studies show scientific evidence that depletion in the total population of dopaminergic neurons takes place when Semaglutide is taken at an optimal dose of 25 nmol/kg. This causes enhancement of lipid peroxidation in striatum & Substantia Nigra. Besides, Semaglutide supports the improvement of motor coordination of the mouse in rotarod apparatus. Loss of neuron is reduced in the region of CA1 & CA3 regions as well as hippocampal dentate gyrus, thereby boosting the motor coordination in walking and hanging tests conducted on a beam at a dose of10nmol/kg. Formulations containing Semaglutide have been used in the treatment of type-II diabetes. With all this scientific data, Semaglutide can be prescribed in the treatment of TYPE-II diabetes.

Dosage Forms [18-21]

Subcutaneous Administration

Oral dosing of this drug for 7 days is recommended in order to replace with subcutaneous administration of injection. 0.25 mg/week is considered to be the initial dose for new patient. In case of continued glycemic control using subcutaneous injection, a dose of 0.5/ week is usually recommended before further increasing to 1 mg / week. The dose at which the action of Semaglutide is maintained will be the range of 0.5 mg/ week to 1 mg/week. It should be noted that the threshold dose to prevent any episode of ADR by Semaglutide is only 1mg/week.

Subcutaneous injection administration after last dose Semaglutide acid tablet is usually recommended by regulatory agencies. Patients administered subcutaneously with 0.5mg/week can be transitioned to 7 or 14 mg orally once a day oral therapy should start up to7 days post the final subcutaneous (SC) injection.

Oral Tablets

Semaglutide must be consumed at a dose of 3mg/day for nearly one month. In case of situations where extra control on glycemic index is required, the dose of Semaglutide can be upgraded to 14 mg/day, which is generally the maximum dose for this formulation. Dose dumping is not acceptable by the sum of two oral formulations of different dose.

Miscellaneous

This drug is also available in the form of prefilled pen injection.

Medical Indications[22]

i. Semaglutide is widely employed in the treatment of type 2 Diabetes mellitus (DM).

ii. Semaglutide is multidimensional in nature by retarding deterioration of function of nephrons and prevent diabetes induced blindness.

iii. Promoting the wellness of cardiovascular system and prevention of episodes of stroke is another important

feature to ponder.

iv. This drug helps in in reducing the effect of meal induced hyperglycemia by enhancing the activity of insulin.

Adverse Effects [23]

Although DPP-4inhibitors are generally well tolerated, they may cause illnesses like nasopharyngitis, Retention of fluid, hepatic and gastric problems and even hypo glycaemic episodes.

Contraindications [24]

The following conditions are contraindicated with Semaglutide:

1. Hyper glycaemia
2. Diabetic retinopathy
3. Decreased kidney function
4. Family history of medullary thyroid carcinoma
5. Pancreatitis
6. Medullary thyroid cancer
7. Multiple endocrine neoplasia Type-II
8. Kidney disease with likely depletion in kidney function

Side effects [25]

Side-effects like emesis, loss of appetite and pain in abdominal regions can take place, which can lead to constipation.

Over Dosage [26]

Any dose consumed equivalent to 4 mg in one sitting is considered to be overdose or dose dumping. The most commonly observed symptom for overdosing of Semaglutide is Nausea. Overdosing of Semaglutide is usually reversible in nature and the supportive treatment must be provided symptomatically. Higher observation time yes you surely required under clinical settings since this drug has long half-life up to one week.

Mild Dose

At milder dose of Semaglutide symptoms like Diaphoresis, Lightheadedness, and Dizziness tends to occur along with probability of tachycardia and palpitations.

Moderate Dose

At moderate doses, episodes of Seizures can occur along with minor neurological illnesses. There is even getting comatosed.

Severe Dose

Serious conditions like Status epilepticus and Cerebral edema can occur with a possibility of hypotension and Ventricular tachycardia.

Pharmacodynamics [27,28]

Semaglutide is considered to be a widely employed glucagon like peptide -1 receptor agonist. The secretion of insulin is improved by promoting the growth and wellness of beta cells of islets of Langerhans. Semaglutide is not only insulinomimetic but is also anti-glucagon analogue.

By enhancing the gastric residence time (GRT), Semaglutide helps in maintenance of homeostasis of serum glucose level in human body. The above pharmacological features are achieved by directly activating and stimulating the glucagon-like peptide secretion by agonizing GLP-1 receptor.

The resemblance of Semaglutide with human glp 1 is above 90%. Loss of weight generally takes place as a result of loss of appetite due to reduced gastric emptying.

Clinical trials [29]

Clinical trials can be defined as the type of experimental studies by which the safety, interaction and toxicity studies of drug is performed in several organisms especially human. This technique is predominantly applied for confirmation of any newly developed medical procedure for drug to be highly effective with broader scope of safety.

Phase	Primary goal
Phase-I	Dose-ranging on healthy volunteers for safety
Phase-II	Drug testing on participants to assess efficacy and side-effects
Phase-III	Testing of drug on participants to assess efficacy, effectiveness and safety
Phase-IV	Post-marketing surveillance in public

Phase-I

This phase of trial is usually conducted in organised clinical setting. Only healthy volunteers are involved in this experimental study. In this phase, 40-80 healthy volunteers are administered with high doses of Semaglutide and constantly monitored. This experimental setup helps in framing the therapeutic window of the drug followed by toxicity and overdosing studies

Phase-II

Volunteers are administered with oral Semaglutide in the range of 2.5 to 40 mg. Bioequivalence studies are conducted for different dosage forms (SC & Oral) of the same drug (Semaglutide). This drug proved to be highly effective in patients with type II Diabetes mellitus with proper tolerance in GIT. A PIONEER- trial was conducted after the victory in the above experimental study. The results were determined in terms of two estimands- trial product & treatment policy. PIONEER- trial usually is comprised of eight clinical trials that determine and compare the safety of Semaglutide to placebo along with the efficacy. Apple near trial is completely randomised and open labelled in nature.

Phase III

Monotherapy

Phase III trial is conducted in the form of PIONEER- one trial to investigate the therapeutic action as monotherapy in more than 700 diabetic patients, who were undergoing sufficient rehabilitation and diet separately.

Randomization was performed in the ratio of 1:1:1:1. The report concluded that the patients with type II Diabetes mellitus had more optimal glucose level as tested by glycosylated hemoglobin test (HbA1C) in comparison with the Placebo. Another phase III study reported that Semaglutide was showing better blood glucose level maintenance within the optimal range in comparison with liraglutide and Placebo after a 1 year trial in nearly 200 patients from Japan with type II diabetes. A PIONEER- 9 trial helped in confirming the above statements in in separate trials thereby, providing better strength to the scientific evidence.

Combination Therapy

The first PIONEER- trial to analyse the therapeutic action and safety of oral Semaglutide-empagliflozin formulation was PIONEER- 2, which was performed in nearly 800 diabetic patients for a time span of 52 weeks. The experimental dose of empaglifozin was 25 mg where as that of Semaglutide was 14 mg. This concluded that Semaglutide has better maintenance of blood glucose levels in comparison with empaglifozin as analysed using glycosylated hemoglobin test. PIONEER- 3 and PIONEER- 7 was conducted to analyse and describe the superior anti-diabetic activity of Semaglutide in comparison with sitagliptin with increased patient population when compared to PIONEER-2. Besides, PIONEER-8 & PIONEER-4 experimental studies were also performed to establish the superiority of Semaglutide over metformin in terms of anti-diabetic activity. All PIONEER trials were conducted for a time span of 365 days.

Some clinical trials was conducted in this phase which wire used to evaluate the therapeutic anti-diabetic activity of Semaglutide in combination with insulin therapy.

Phase-IV

Phase IV is defined as the class of clinical trial, which generally observes the adverse drug reactions (ADR) occurred over a period of time in patients, who undergoes modern therapy other than those mentioned in the previous phases of clinical trials. Any new side effect for ADR will be registered and proper supportive care will be discussed. Since this phase takes place even after the marketing of the drug, this is better known as post marketing surveillance (PMS).

	Baseline	Mean reduction in A1C(%)				Percentage achieving A1C < 7%			
		Semaglutide			Comparator	Semaglutide			Comparator
		3 mg	7 mg	14mg		3 mg	7 mg	14mg	
PIONEER-1	8.0	–0.9	–1.2	–1.4	–0.3	55	69	77	31
PIONEER-2	8.1			–1.3	–0.9			67	40
PIONEER-3	8.3	–0.6	–1.0	–1.3	–0.8	27	42	55	32
PIONEER-4	8.0			–1.2	–1.1(liraglutide)			68	62(liraglutide)
PIONEER-5	8.0			–1.0	– –0.2			58	23
PIONEER-7	8.3	–1.3 (flexdosing)			–0.8	58 (flexdosing)			25
PIONEER-8	8.2	–0.6	–0.9	–1.3	–0.1	28	43	58	7
PIONEER-9	8.2	–1.1	–1.6	–1.8	–1.4(liraglutide)	52	69	81	53(liraglutide)
PIONEER-10	8.3	–1.1	–1.7	–2.0	–1.5	46	75	82	70

	Baseline	Mean reduction in A1C (%)				Percentage achieving A1C < 7%			
		Semaglutide			Comparator	Semaglutide			Comparator
		3 mg	7 mg	14 mg		3 mg	7 mg	14 mg	
PIONEER-1	8.0	–0.8	–1.3	–1.5	–0.1	59.1	71.9	80.3	33.8
PIONEER-2	8.1			–1.4	–0.9			70.3	40.7
PIONEER-3	8.3	–0.5	–1.1	–1.4	–0.8	27	42	55	32
PIONEER-4	8.0			–1.3	1.1(liraglutide)			72	65 (liraglutide)
PIONEER-5	8.0			–1.1	–0.1			56	16
PIONEER-7	8.3	–1.4 (flexdosing)			–0.7	63 (flexdosing)			28
PIONEER-8	8.2	–0.6	–1.0	–1.4	–0.0	19.8	27.4	49.3	2.5
PIONEER-9	8.2	–1.1	–1.5	–1.7	–1.4 (liraglutide)	56	73	80	53 (liraglutide)
PIONEER-10	8.3	–1.1	–1.7	–2.0	–1.6	46	76	84	73

Semaglutide as a Multi-Dimensional Drug [30]

Semaglutide can also be considered as drug used in treatment of cardiovascular ailments like atherosclerosis other than anti-diabetic effect. Administration of this drug at a dose ranging between 0.5 and 1 mg can help in preventing episodes of myocardial infarction (MI). The hundred- and 4-week trial also inferred that systolic and diastolic pressure is maintained at optimal range thereby reducing the probability of hypertension. Consistent performance of Semaglutide is observed in maintenance of cardiovascular illnesses like myocardial infarction atherosclerosis hypertension, etc. Conclude that it is very effective cardiovascular agent in comparison with empagliflozin.

CONCLUSION

Out of the oral GLP-1 agonizing agents, Semaglutide emerges to be one of the best drugs with anti-diabetic activity. The safety profile of oral Semaglutide is also looking greater in comparison with other members of the same class. Even though oral Semaglutide did not diminish the incidence of the complex primary endpoint in the PIONEER--6 trial, a reduction in cardiovascular and all-cause mortality was observed. Therefore, oral Semaglutide appears to represent a useful tool in the management of patients with TIIDM, predominantly those with established CVD or high cardiovascular risk and reluctant to receive injectable GLP-1 receptor agonists. Future studies should further evaluate the effects of oral Semaglutide on both cardiovascular events and the micro vascular complications of TIIDM. In addition, studies in specific subgroups, including those with and without established cardiovascular disease as well as in those with diabetic nephropathy, will augment new insights into the role of this agent in the management of TIIDM.

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