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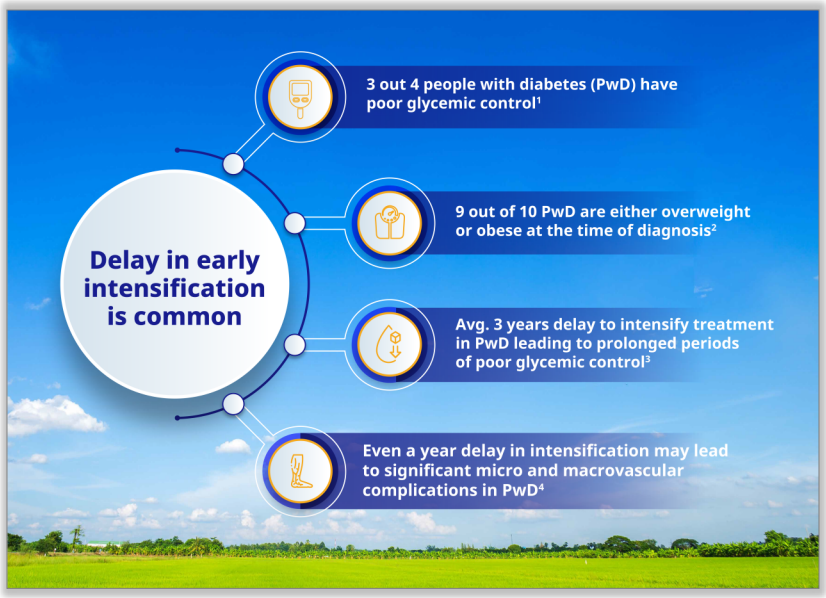
Early initiation with oral semaglutide

Problem Statement

- **3 out of 4 people with diabetes have poor glycaemic control** (HbA1c>7%)
- Moreover, **90% of the people with diabetes are either overweight or obese** at the time of diagnosis of diabetes itself.
- Excess weight is closely related to the onset and progression of diabetes.
- Excess weight can result in increased insulin resistance and leads to fluctuations in blood glucose levels which makes it difficult to manage diabetes effectively.
- Excessive weight can lead to hypertension, dyslipidemia, and other cardiovascular risk factors, which can worsen the prognosis for individuals with diabetes.
- On an average it **takes 3 years to intensify** or step-up diabetes treatment. It means that if the person is on 1 OAD, it takes at least 3 years to get intensified to 2 OADs. This may result in the person with diabetes to be on prolonged periods of poor glycaemic control.
- Prolonged periods of poor glycaemic control (HbA1c>7%) leads to microvascular and macrovascular complications of diabetes.



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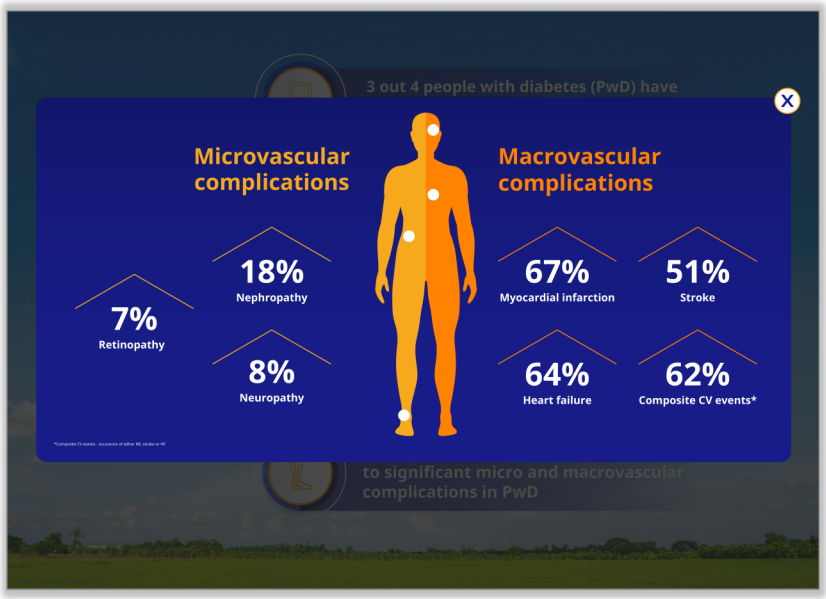
Problem Statement

- Even one year delay in stepping up treatment or intensifying the treatment can result in increased risk of complications like -
  - 18% Nephropathy
  - 8% Neuropathy
  - 7% Retinopathy
  - 67% Myocardial infarction (MI)
  - 64% Heart failure (HF)
  - 51% Stroke

- Poor control of diabetes results in some irreversible changes to the blood vessels and body cells which then predisposes or progresses to long-term complications.

- Landmark studies in diabetes like DCCT & UKPDS showed - Early, intensive treatment of diabetes aimed at tight glucose control reduces the future risk of microvascular and macrovascular complications - "Metabolic memory" or **"legacy effect"**



*(Composite CV events - occurrence of either MI, stroke or HF)

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Concept of Early Initiation

DCCT

Objective: To examine if intensive treatment with the goal of maintaining blood glucose concentrations close to the normal range could decrease the frequency and severity of microvascular and neurologic complications of T1D. Methods: Data were collected from 1983 to 1989; 1441 patients with T1D were randomly assigned to intensive therapy and followed for a mean of 6.5 years; mean baseline A1C ranged between 8.8% and 9.0%, and patients were assessed regularly for retinopathy progression and other complications. Conclusion: In patients with T1D, intensive therapy effectively delays onset and slows the progression of onset for diabetic retinopathy, nephropathy, and neuropathy.

UKPDS

Objective: To compare the effects of intensive blood-glucose control vs conventional treatment on the risk of microvascular and macrovascular complications in patients with newly diagnosed T2D. Methods: Data were collected from 1977 to 1991. Randomized controlled trial of 3,867 newly diagnosed patients with T2D (median age 54 years) randomly assigned to intensive treatment with sulfonylureas or insulin vs conventional therapy (primarily diet). Additionally, 753 patients were randomized to receive metformin vs conventional therapy. Mean baseline A1C ranged from 6.1% to 7.1%. The 3 aggregate endpoints were: any diabetes-related endpoint, diabetes-related death, and all-cause mortality. Conclusion: Intensive blood glucose control substantially decreased the risk of microvascular complications, but not macrovascular disease, in patients with T2D

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Guideline Recommendations Supporting Early Initiation with GLP-1RA

- Diabetes guidelines have evolved from a traditional glucocentric approach to cardio-renal-metabolic approach in managing newly diagnosed type 2 diabetes
- Targeting weight early in type 2 diabetes can promote sustained glycemic control, positively impact the cardiometabolic risk factors, disrupt the underlying pathophysiology and slow down/ reverse the disease progression leading to reduced risk of complications.
- The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) consensus statement 2022 recommends giving equal weightage to weight management and glucose control in patients with type 2 diabetes.
- ADA 2024 guidelines for the management of type 2 diabetes recommend early initiation with GLP-1RA having high to very-high efficacy like Semaglutide for heart/kidney protection, glucose control, and weight loss.
- ESC 2023 guidelines recommend for early initiation with GLP-1RA with proven CV safety or benefit like Semaglutide to reduce the CV risk in people with type 2 diabetes independent of glucose control.

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Benefits of Early Initiation with GLP-1RA

- Early initiation with GLP-1RA refers to starting GLP-1RA early in the course of type 2 diabetes (as early as within 1 year and not more than 10 years of diagnosis of diabetes or as first/second line of therapy)

- Early initiation with GLP-1RA may provide a host of benefits like –

  - Greater reduction of HbA1c from the baseline
  - Increased likelihood of achieving target HbA1c <7%
  - Greater reduction of weight from the baseline
  - Increased likelihood of achieving weight loss >5%
  - Sustained glycaemic control (risk of moving out of target HbA1c of 7% is significantly reduced or prolong time to treatment failure)
  - Improved beta cell function and delay the progression of diabetes
  - Lower risk of micro and macrovascular complications

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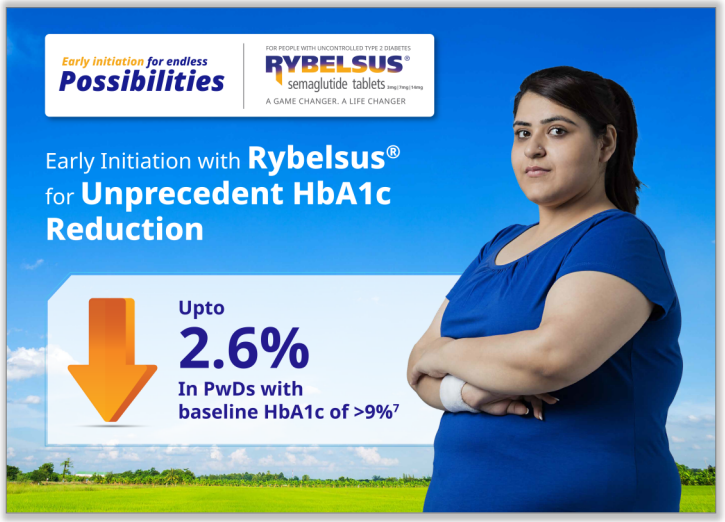
Evidence with Early Initiation with Oral Semaglutide

- Oral semaglutide has demonstrated an unprecedented HbA1c reduction of **upto 1.5% and unsurpassed weight loss of upto 5 kg without increasing the risk of hypoglycemia** in PIONEER clinical trials
- Oral semaglutide has shown consistent **CV safety with 21% MACE reduction, 49% reduction in all-cause mortality** and **51% reduction in CV death** (PIONEER 6)
- Oral semaglutide exerted beneficial effects on body weight and body composition by appetite suppression, reducing fat mass and preserving muscle mass. Studies have shown that there is a **3-fold greater loss of fat over lean body mass observed with semaglutide.**
- Oral semaglutide also reduced waist circumference **upto 4.7 cms, an independent predictor of atherosclerotic CVD (ASCVD) risk.**
- Oral semaglutide is now approved in India as first line therapy management of type 2 diabetes as an adjunct to diet and exercise



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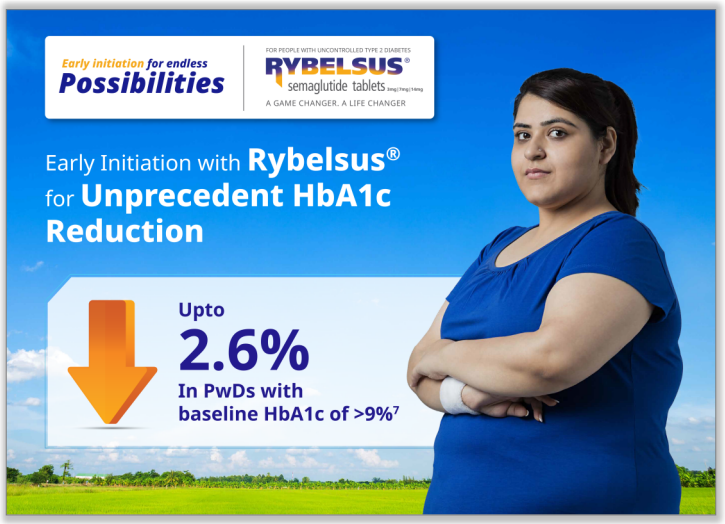
Evidence with Early Initiation with Oral Semaglutide

Early initiation with oral semaglutide
(PIONEER 1 post hoc analysis) showed -

- **8 out of 10 patients achieved glycaemic target of HbA1c<7%** when oral semaglutide is initiated within 1 year of T2D diagnosis.
- **1 in 3 patients achieved a weight loss > 5%** when oral semaglutide is initiated within 1 year of T2D diagnosis.
- In patients with baseline A1C of >9%, initiation with oral semaglutide can **reduce A1C upto 2.6%**.



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Evidence with Early Initiation with Oral Semaglutide

- >50% of patients achieved pharmacological remission (defined as achieving near normal HbA1c level of <6.5% with pharmacological therapy) when oral semaglutide was added to their existing therapy within 10 years of T2D diagnosis. (PreCare2 study)

- SELECT study with Inj. Semaglutide 2.4 mg showed that early weight loss can -

Induce diabetes regression (pre-diabetes to normoglycemia)

Reduce diabetes progression (pre-diabetes to diabetes)

~80% of the participants who had 5-10% body weight loss with Inj. Sema 2.4 mg OW regressed from a prediabetic range (A1C >5.7 to <6.5) at baseline to normoglycemia (A1C<5.7).

Proportion of participants who progressed from prediabetic range (A1C >5.7 to <6.5) at baseline to diabetes (A1C >6.5) is ~3 times lesser in those who had 5-10% body weight loss with Inj. Sema 2.4 mg OW.

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Evidence with Early Initiation with Oral Semaglutide

Pioneer 1 Study Synopsis

Early achievement of near-normal HbA1c is associated with a reduced risk of future complications in type 2 diabetes (T2D) and may help motivate patients (pts) to maintain treatment. We conducted a post-hoc analysis of the PIONEER 1 study to look at the impact of early initiation of oral semaglutide (sema) on glycemic efficacy, body weight (BW), and achievement of targets. Pts on diet and exercise were randomized to oral sema 3, 7, or 14 mg once daily, or placebo (pbo). HbA1c and BW reduction, and achievement of HbA1c targets (<7%, ≤6.5%, <6%) were assessed at 26 weeks in pts with T2D duration ≤1 year and >1 year for comparison. Greater HbA1c and BW reductions were seen for oral sema 14 mg vs pbo for both duration ≤1 year (−1.6% vs −0.4%; −4.3 kg vs −1.6 kg) and >1 year (−1.4% vs 0.2%; −4.0 kg vs −1.4 kg); the subgroup interaction (≤1 vs >1 year) was significant for HbA1c (p=0.04) but not BW. A high proportion of pts initiating oral sema within ≤1 year of T2D diagnosis reached glycemic targets, including HbA1c <6.0% in 45% of pts on oral sema 14 mg (vs 31% in the >1year group; Figure); subgroup interactions were not significant. In conclusion, initiation of oral sema in pts within ≤1 year of T2D diagnosis resulted in robust HbA1c and BW reductions, and attainment of glycemic targets, including near-normal HbA1c

PreCare2 Study

Observational, real-world, study aimed to investigate the efficacy of the combination therapy with dapaglifozin and oral semaglutide over glycemic control. Data of 1335 patients with type 2 diabetes followed by 11 Diabetes centers in Lombardia, Italy. A group of 443 patients was treated with dapagliflozin alone, the other group of 892 patients was treated with the combination therapy of dapagliflozin plus oral semaglutide. Both groups of patients showed an improvement of glycometabolic control after 6 months of treatment; indeed, the treatment with dapagliflozin plus oral semaglutide showed a reduction of glycated hemoglobin of 1.2% as compared to the 0.5% reduction observed in the dapagliflozin alone group. Significant changes were observed in body mass index, fasting plasmatic glucose, blood pressure, total cholesterol, LDL and albumin to creatinine ratio, with a high rate (55%) of near-normalization of glycated hemoglobin. Our real world data confirmed the potential of the oral combination therapy dapagliflozin with semaglutide in inducing pharmacological remission of type 2 diabetes mellitus.

SELECT Study Synopsis

Double-blinded trial compared subcutaneous once-weekly semaglutide 2.4 mg with placebo as an adjunct to standard of care for prevention of major adverse cardiovascular events (MACEs) over a period of up to five years. The trial enrolled 17,604 adults aged 45 years or older with overweight or obesity and established cardiovascular disease (CVD) with no prior history of diabetes. The trial achieved its primary objective by demonstrating a statistically significant and superior reduction in MACE of 20% for people treated with semaglutide 2.4 mg compared to placebo. ~80% of the participants who had 5-10% body weight loss with Inj. Sema 2.4 mg OW for 156 weeks regressed from a prediabetic range (A1C >5.7 to <6.5) at baseline to normoglycemia (A1C<5.7). Proportion of participants who progressed from prediabetic range (A1C >5.7 to <6.5) at baseline to diabetes (A1C >6.5) is ~3 times lesser in those who had 5-10% body weight loss with Inj. Sema 2.4 mg OW.