CLINIC-*Sim*

Simulating a Patient-Centered Approach to Optimize Early Glycemic Control and Weight Management in Type 2 Diabetes

Supporting Early Glycemic Control and Weight Management Through Shared Decision-Making

Supporting Early Glycemic Control for Patients With T2D

HCPs can support their patients by **assessing goals**, **advising**, and **escalating** to appropriate type 2 diabetes pharmacotherapy when necessary

The ADA-EASD Consensus Report recommends several strategies for patients, including:

- Assessing HbA_{1c} every 3 months for patients who are not at glycemic targets
- Intensifying treatments when therapy goals are not met
- In the absence of other comorbidities requiring more frequent monitoring, patients who have achieved glycemic targets can be assessed every 6 months

Davies MJ, et al. *Diabetes Care*. 2022;45(11):2753-2786.

Strategies to Foster Empathy and Trust with Patients: Co-Create Goals

Rationale:
Using common language to discuss treatment goals results in greater clarity and impact

ASK

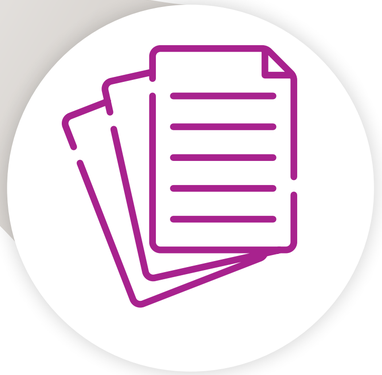
Your patients questions about their goals

PROBE

To clarify the questions

REPEAT

Words or expressions you heard back to the patients



RECORD

In chart for future exchanges

5As of Weight Management

Obesity is a chronic, relapsing, and progressive disease, characterized by abnormal or excessive accumulation of adiposity that presents a risk to health[1,2]

How an individual develops obesity and how they will respond to interventions involves a complex interaction of genetic, biological, environmental, and behavioral factors[3]

Successful obesity management requires identifying and addressing the 'root causes' of weight gain and barriers to weight management[4]

ASK
for permission to discuss weight and explore readiness

ASSESS
obesity-related risks and potential "root causes" of weight gain

ADVISE
on health risks and treatment options

AGREE
on health outcomes and behavioral goals

ASSIST
in accessing appropriate resources and providers and arrange follow-up

1. https://www.who.int/health-topics/obesity#tab=tab_1 (Accessed August 28, 2023). 2. Sbraccia P. *Intern Emerg Med.* 2023;18:1-5. 3. https://obesitycanada.ca/resources/tools-accessing-health-care/# (Accessed August 28, 2023).
4. https://obesitycanada.ca/wp-content/uploads/2022/03/Practitioner_Guide_Personal_Use-edited.pdf (Accessed August 28, 2023).

Use of Appropriate Language with Patients[1,2]

Appropriate use of language is a simple, implementable technique clinicians can use to lower the patient's anxiety, build confidence, and support self-care.[2]

Fosters patient-clinician collaboration

Ask open-ended questions that are not directly related to body weight

"What concerns you about your health today?"

Click here to see an example

Encourages engagement

When body weight is raised while addressing the patient's health concerns, it enhances patient engagement

Obesity is associated with several medical conditions, allowing for an easier transition to discuss body weight

Supports empathy and trust

Use non-medical language to discuss diabetes treatment goals to maintain patient comfort and engagement

E.g., how does the patient describe the impact of diabetes on their lives?

1. American Diabetes Association. *Diabetes Care*. 2022;45(1):S1-S264. 2. https://www.england.nhs.uk/wp-content/uploads/2018/06/language-matters.pdf (Accessed September 28, 2022).

Use of Appropriate Language with Patients[1,2]

An example of patient-clinician communication

Clinician: What concerns do you have about your health today?

Patient: My knees have been bothering me lately and I've been having trouble sleeping...

Clinician: Thank you for letting me know about your knee pain and sleep issues. It's important to address these symptoms. They can sometimes be connected to underlying heath conditions. Would it be okay if we discussed potential factors that might contribute to your symptoms?

Patient: Yes.

Clinician: It's worth considering that maintaining a healthy weight can often have a positive impact on knee pain and sleep quality. Many people have similar concerns, and they find that addressing them can improve their overall well-being. Would you be willing to talk about your weight? What are your thoughts about your weight right now?

Patient: Yes, when I was younger and my body weight was lower than it is now, I had more energy. Now I am too exhausted to get up and exercise.

Clinician: Would you be willing to work together and create a new treatment plan that feels manageable to you? You'll have less knee pain, better sleep, and more energy again.

Patient: Okay, I'm willing to try.

https://healthysd.gov/wp-content/uploads/2014/12/2014ObesityToolkit.pdf (Accessed August 22, 2023).

Patient Profile at Visit #1 *(at time of diagnosis)*

Patient Profile

- 47-year-old African American female
- Diagnosed with T2D 9 months ago
- HbA_{1c} since diagnosis: 8.7%
- Current treatment: 1000 mg metformin daily at diagnosis
- Followed by registered dietitian/ nurse educator

Medical History

- Prediabetes for 2 years preceding diagnosis, tried to manage with diet and exercise
- Gestational diabetes with her second child
- Hypertension
- Obesity
- Mixed dyslipidemia

Family History

- T2D in father, maternal aunt
- CAD in father
- Hypertension in mother and father

Social History

- Married, has 2 children, ages 10 and 15
- Never smoked or vaped, no illicit substances, rarely drinks alcohol
- High school math teacher

Physical Exam and Labs

Normal eGFR,
normal urine microalbumin

BMI: 33 kg/m^2 (195 lbs)

Blood pressure: 145/90 mmHg

Total cholesterol: 210 mg/dL

LDL cholesterol: 109 mg/dL

HDL cholesterol: 44 mg/dL

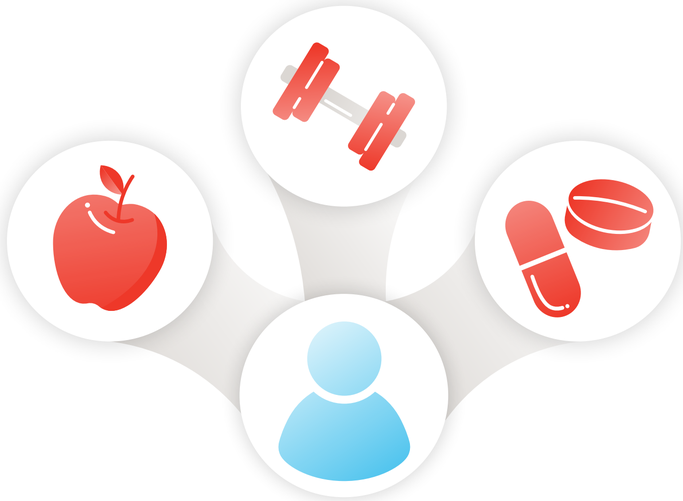
Triglycerides: 290 mg/dL

BMI=Body Mass Index; eGFR=Estimated Glomerular Filtration Rate; HDL=High-Density Lipoprotein; LDL=Low-Density Lipoprotein.

Visit #2 *(9 months)*

- The patient was diagnosed with type 2 diabetes, and her HbA_{1c} was 8.7% at the time. She was started on 1000 mg metformin daily. During that visit, she was advised on lifestyle modifications, including dietary changes to help both her diabetes and hypertension management, as well as recommendations to incorporate exercise. She was encouraged to start a statin for dyslipidemia but was too overwhelmed by her diabetes and declined statin therapy.

- At visit 2, her HbA_{1c} decreased to 7.9%. She again declined a statin and agreed to start an ACE inhibitor. Her metformin was titrated to 1500 mg total daily dose.



ACE=Angiotensin-Converting Enzyme.

Visit #3 - 4-month follow-up *(13 months since diagnosis)*

- She returns 4 months later.
- She is taking a dose of 1500 mg metformin daily (500 mg in the morning and 1000 mg in the evening) without missing doses. She was not able to tolerate a dose of 1000 mg twice daily. Her HbA_{1c} has decreased to 7.7% from 7.9%, and her body weight remained stable.
  - BMI: 33 kg/m^2 (195 lbs)
  - Blood pressure: 130/85 mmHg
  - Total cholesterol: 205 mg/dL
  - LDL cholesterol: 110 mg/dL
  - HDL cholesterol: 43 mg/dL
  - Triglycerides: 260 mg/dL

- She increased her physical activity by parking farther and trying to walk more but often struggles to find the time to get more exercise in.
- She tries to eat more balanced meals with protein, vegetables, and fewer carbohydrates; she finds it difficult to make multiple meals for her family members, who prefer to keep to their old dietary routine.
- She is motivated to continue working on lifestyle changes and has agreed to start a statin.

Decision Point 1: In addition to continuing metformin 1500 mg daily, which of the following may be the next best step?

A Continue lifestyle modifications – she is very motivated and prefers not to start another medication

B Start a sulfonylurea and continue lifestyle modifications

C Start an incretin receptor agonist and continue lifestyle modifications

D Start a DPP-4 inhibitor

DPP-4=Dipeptidyl Peptidase-4.

Decision Point 1: In addition to continuing metformin 1500 mg daily, which of the following may be the next best step?

Continue lifestyle modifications – she is very motivated and prefers not to start another medication

Incorrect – there may be a better option for this patient. Lifestyle modifications, including healthy nutrition, physical activity, and weight management, are important, and she has room for improvement. However, it is important to consider these changes take time, and biologic factors contributing to obesity and high HbA_{1c} may necessitate the addition of pharmacotherapy with lifestyle changes to achieve targets. To optimally reduce her potential risk of future diabetes complications, achieving glycemic control as early as possible is very important.

Davies MJ, et al. *Diabetes Care.* 2022;45(11):2753-2786.

DPP-4=Dipeptidyl Peptidase-4.

Decision Point 1: In addition to continuing metformin 1500 mg daily, which of the following may be the next best step?

Continue lifestyle modifications – she is very motivated and prefers not to start another medication

Incorrect – there may be a better option for this patient. While sulfonylureas are effective for glucose control, the potential disadvantages of this therapy may outweigh the benefits for this patient. Specifically, sulfonylureas:

- Lack a durable effect
- Increase the risk of hypoglycemia
- Are associated with weight gain

The guidelines currently favor treatments with additional non-glucose-lowering effects, and an overall better safety profile. Given that this patient has obesity as well as taking into consideration current guideline recommendations for pharmacotherapy, an agent with additional benefits beyond glycemic control is likely to be more beneficial.

Davies MJ, et al. *Diabetes Care*. 2022;45(11):2753-2786.

DPP-4=Dipeptidyl Peptidase-4.

Decision Point 1: In addition to continuing metformin 1500 mg daily, which of the following may be the next best step?

A Continue lifestyle modifications – she is very motivated and prefers not to start another medication

Correct – this may be an appropriate option for this patient.

According to the ADA/EASD Consensus Report, incretin receptor agonists have high to very high efficacy for glucose lowering. Concomitant use of an incretin receptor agonist with an insulin secretagogue or insulin may increase the risk of hypoglycemia.

ADA=American Diabetes Association; EASD=European Association for the Study of Diabetes.
Davies MJ, et al. *Diabetes Care.* 2022;45(11):2753-2786.

D Start a DPP-4 inhibitor

DPP-4=Dipeptidyl Peptidase-4.

Decision Point 1: In addition to continuing metformin 1500 mg daily, which of the following may be the next best step?

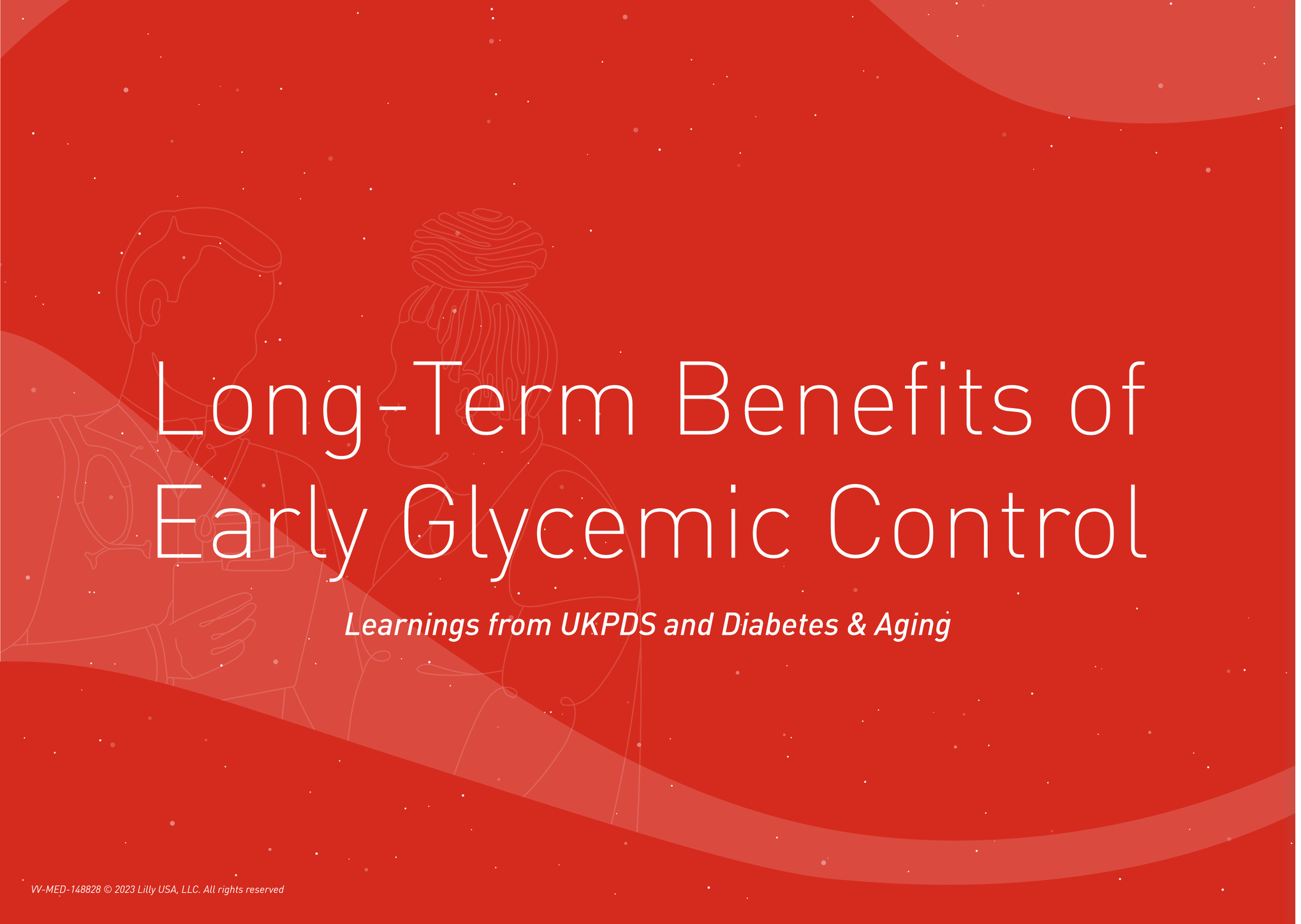
A Continue lifestyle modifications – she is very motivated and prefers not to start another medication

Incorrect – there may be a better option for this patient. According to the ADA/EASD Consensus Report, DPP-4 inhibitors have modest glucose-lowering efficacy and a neutral effect on weight. Therefore, in this individual with uncontrolled type 2 diabetes and obesity, a DPP-4 inhibitor would not be the best choice.

ADA=American Diabetes Association; DPP-4=Dipeptidyl Peptidase-4; EASD=European Association for the Study of Diabetes.
Davies MJ, et al. *Diabetes Care.* 2022;45(11):2753-2786.

D Start a DPP-4 inhibitor

DPP-4=Dipeptidyl Peptidase-4.



Long-Term Benefits of Early Glycemic Control

Learnings from UKPDS and Diabetes & Aging

The ADA-EASD Guidelines Recommend Early Intervention to Achieve Glycemic Targets

> Attaining recommended glycemic targets yields substantial and enduring reductions in the onset and progression of microvascular complications, and ***early intervention*** is essential

> A reasonable HbA_{1c} .... to see microvascular benefits (generally 10 years) is around 53 mmol/mol (7%) or less. ***Aiming for a lower HbA_{1c} level than this may have value if it can be achieved safely*** without significant hypoglycemia or other adverse treatment effects.

Davies MJ, et al. *Diabetes Care*. 2022;45(11):2753-2786.

ADA-EASD Guidelines Outline Medications for Glycemic Control and Weight Management as Adjuncts to Lifestyle Interventions[1,2]

Goal | Achievement and Maintenance of Glycemic and Weight Management Goals

Glycemic Management: Choose approaches that provide the efficacy to achieve goals

Efficacy for Glucose Lowering[1]

VERY HIGH
- Dulaglutide (high dose)
- Semaglutide
- Tirzepatide
- Insulin
- Combination oral
- Combination injectable (GLP-1 RA/insulin)

HIGH
- GLP-1 RA (not listed above)
- Metformin
- SGLT-2 inhibitor
- SU
- TZD

INTERMEDIATE
- DPP-4 inhibitor

Achievement and Maintenance of Weight Management Goals:

Efficacy for Weight Loss[1]

VERY HIGH
- Semaglutide
- Tirzepatide

HIGH
- Dulaglutide
- Liraglutide

INTERMEDIATE
- GLP-1 RA (not listed above)
- SGLT-2 inhibitor

NEUTRAL
- DPP-4 inhibitor
- Metformin

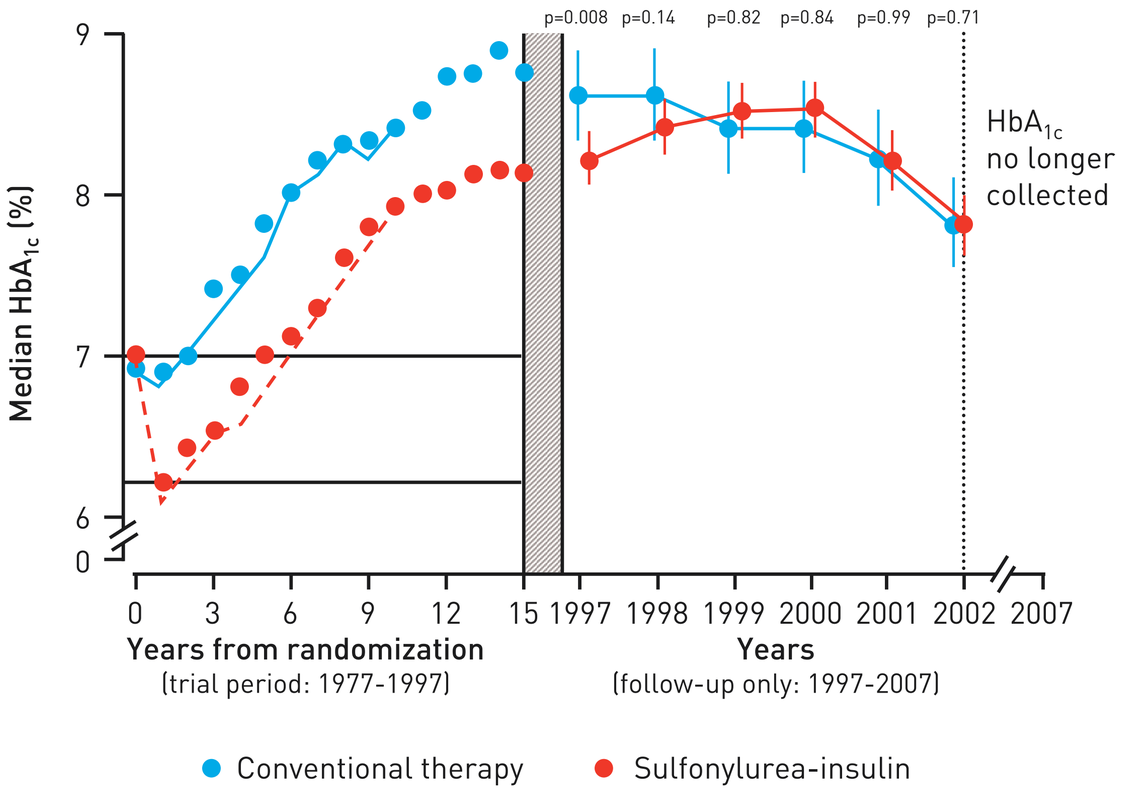
Medications for the management of T2D can have varying effects on clinical outcomes, including body weight, that vary between, and sometimes within, drug classes[2]

DPP-4=Dipeptidyl Peptidase-4; GLP-1 RA=Glucagon-Like Peptide-1 Receptor Agonist; SGLT-2=Sodium-Glucose Cotransporter-2; SU=Sulfonylurea; TZD=Thiazolidinedione.

1. Davies MJ, et al. *Diabetes Care.* 2022;45(11):2753-2786. 2. Apovian CM, et al. *Adv Ther.* 2019;36:44-58.

Early Intensive Glycemic Control Is Associated With Decreased Risk of Type 2 Diabetes-Related Complications[1-3]

Long-term Follow-up and Legacy Effect



In the UKPDS trial:

Historical HbA_{1c} values have a **greater impact** than recent values on all-cause mortality, myocardial infarction, and microvascular disease

Results from the 10-year post-trial follow-up showed:

13% risk reduction in all-cause mortality (p=0.007)

15% risk reduction in myocardial infarction (p=0.01)

24% risk reduction in microvascular disease (p=0.001)

UKPDS=The UK Prospective Diabetes Study.

1. UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352(9131):837-853. 2. Holman RR, et al. *N Engl J Med*. 2008;359(15):1577-1589. 3. Lind M, et al. *Diabetes Care*. 2021 Oct 1;44(10):2231-7.

Improved Glycemic Control Lowers the Risk of Microvascular and Macrovascular Complications

DCCT/EDIC study[1,2]

Among patients with type 1 diabetes, initial intensive glycemic therapy and comprehensive care improved glycemia and overall outcomes during long-term follow-up

Although DCCT/EDIC was conducted in patients with T1D, the consequences of hyperglycemia are similar in T1D and T2D. Similar to UKPDS, this trial highlights the importance of early glycemic control on long-term outcomes in diabetes.

DCCT/EDIC=Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications; T1D=Type 1 Diabetes; T2D=Type 2 Diabetes.

1. Nathan DM, et al. *N Engl J Med* 2005;353:2643-53. 2. DCCT/EDIC study research group. *Diabetes Care* 2016;39:686-93.

Improved Glycemic Control Lowers the Risk of Microvascular and Macrovascular Complications

DCCT/EDIC

To determine whether intensive therapy compared with conventional therapy during the Diabetes Control and Complications Trial affected the incidence of cardiovascular disease over 30 years of follow-up

1441 people with type 1 diabetes were enrolled in DCCT

1423 subjects joined the long-term EDIC follow-up

Conventional therapy
» One or two daily insulin injections

Intensive therapy
» Three or more daily insulin injections or treatment with an external insulin pump

Follow up only:
standard-of-care therapy

Diabetes Control and Complications Trial (DCCT)
1983-1993

Epidemiology of Diabetes Interventions and Complications (EDIC)
1994-2005

DCCT=Diabetes Control and Complications Trial; EDIC=Epidemiology of Diabetes Interventions and Complications.

1. Nathan DM, et al. *N Engl J Med* 2005;353:2643-53. 2. DCCT/EDIC study research group. *Diabetes Care* 2016;39:686-93.

In DCCT/EDIC, Improved Glycemic Control Lowers the Risk of Microvascular and Macrovascular Complications

During 30 years of follow-up:

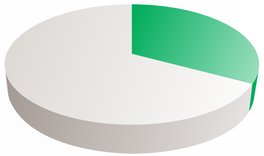
149 CV events
in 82 former intensive treatment participants

217 CV events
in 102 former conventional treatment participants

Macrovascular risk reduction with intensive versus conventional treatment:

↓30% risk reduction for the first CV event[2]

↓32% risk reduction for the first occurrence of MACE (nonfatal MI, stroke or CV death)[2]



Intensive glycemic therapy is associated with microvascular benefit:

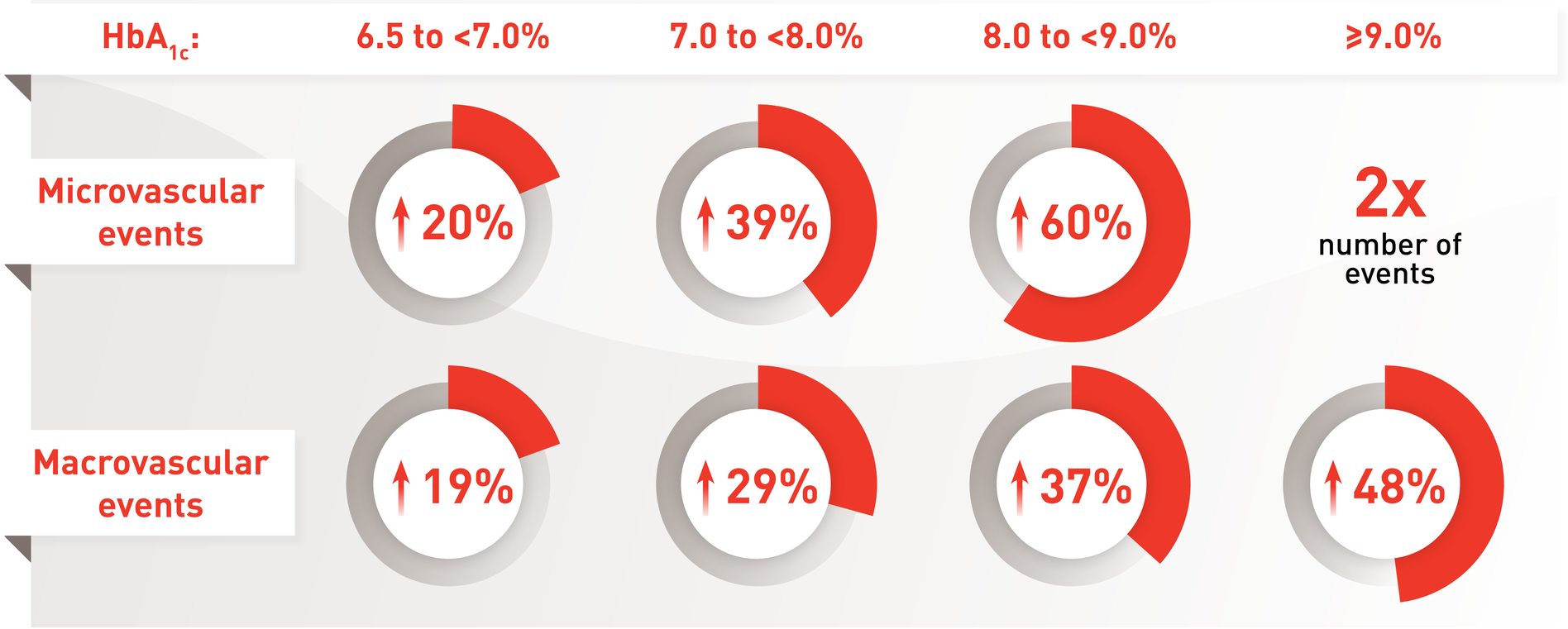
↑ prevalence of microalbuminuria in the conventional group at EDIC year 11

CV=Cardiovascular; DCCT/EDIC=Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications; MACE=Major Adverse Cardiovascular Event; MI=Myocardial Infarction.

1. Nathan DM, et al. *N Engl J Med* 2005;353:2643-53. 2. DCCT/EDIC study research group. *Diabetes Care* 2016;39:686-93.

Achieving HbA_{1c} <6.5% in the First Year After Diagnosis Was Associated With a Lower Risk of T2D Complications

In the <u>Diabetes & Aging study</u>: Compared with HbA_{1c} levels <6.5%, patients with HbA_{1c} ≥6.5% in the first year had a higher risk for microvascular and macrovascular events



Longer periods of exposure to HbA_{1c} 6.5-8% did not increase risk of micro- or macrovascular events during follow up

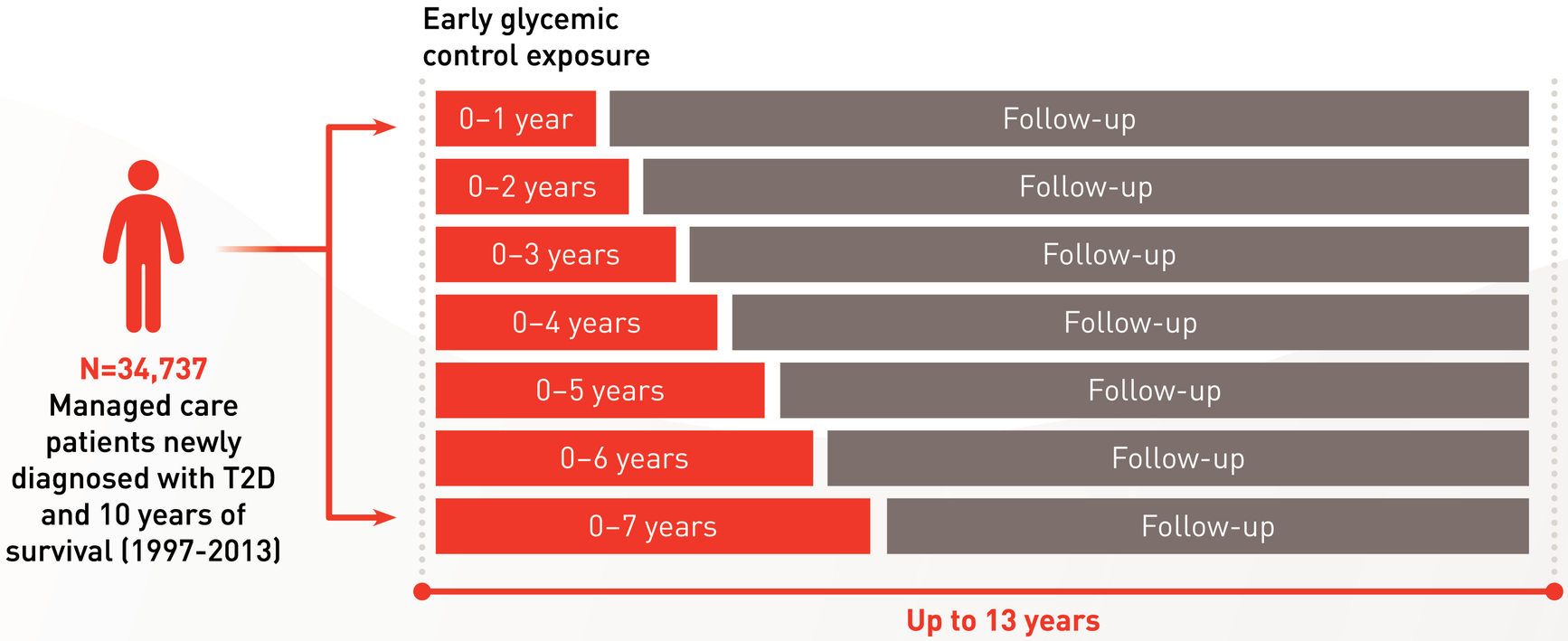
Laiteerapong N, et al. *Diabetes Care.* 2019;42(3):416-426.

Achieving HbA_{1c} <6.5% in the First Year After Diagnosis Was Associated With a Lower Risk of T2D Complications

In the Diabetes & Aging study: Compared with HbA_{1c} levels <6.5%, patients with HbA_{1}

Diabetes & Aging

To examine for a legacy effect of early glycemic control on diabetic complications and death



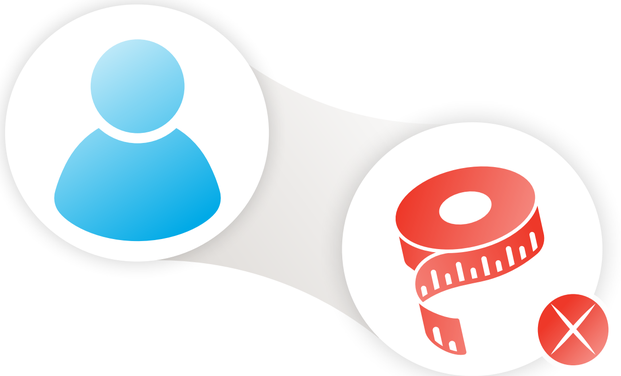
T2D=Type 2 Diabetes.

Laiteerapong N, et al. *Diabetes Care*. 2019;42(3):416-426.

Visit #4 – 3-month follow-up *(16 months after diagnosis)*

- At her last visit, you discussed all options. Although she began to understand the importance of early glycemic control, she was hesitant to start another medication, especially an injectable therapy.
- She has made some progress on lifestyle modifications. She and her husband are going on a 30-minute walk four days a week after dinner, and her kids are participating in preparing healthy dinners with her.

- She is happy that her HbA_{1c} has not increased and is down to 7.4%, but she is concerned about her weight and the potential health consequences of excess weight.
- BMI remains at 33 kg/m^2.



Decision Point 2: Which of the following may be the next best step?

A She is again reluctant to add another medication. Continue metformin and lifestyle modifications with additional counseling

B Review the potential benefits of early glycemic control and potential additional non-glycemic benefits again at this visit and suggest adding an incretin receptor agonist to her current regimen of 1500 mg metformin daily

Decision Point 2: Which of the following may be the next best step?

She is again reluctant to add another medication. Continue metformin and lifestyle modifications with additional counseling

Incorrect – there may be a better option for this patient. While lifestyle modifications are a cornerstone to optimizing blood glucose and weight management in people with type 2 diabetes, many metabolic and hormonal processes make achieving target glycemic and weight control with lifestyle alone difficult and sometimes impossible without pharmacotherapy.

Evidence suggests the patient may likely experience disease progression on metformin monotherapy. In addition to missing the potential key benefits of early effective glycemic control, metformin alone may not provide the added weight loss benefit that may be achieved with one of the other agents.

Kahn SE, et al. *New England Journal of Medicine.* 2006 Dec 7;355(23):2427-43.

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Decision Point 2: Which of the following may be the next best step?

She is again reluctant to add another medication. Continue metformin and lifestyle modifications with additional counseling

Correct – this may be an appropriate option for this patient.

According to the ADA/EASD Consensus Report, glucose-lowering therapies with high to very high dual glucose and weight efficacy are preferred for patients with type 2 diabetes, given the importance of early and sustained glycemic control.

ADA=American Diabetes Association; EASD=European Association for the Study of Diabetes.

Davies MJ, et al. *Diabetes Care*. 2022;45(11):2753-2786.

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Optimizing Early Glycemic Control Using Combination Therapy or Very High-Efficacy Monotherapy

Type 2 Diabetes Progression on Monotherapy

Learnings from UKPDS[1-4]

Among **newly diagnosed** patients with type 2 diabetes receiving **diet, metformin, sulfonylurea** or **insulin:**

HbA_{1c} progressively increases over time on monotherapy despite an initial decrease in the first year[1,2]

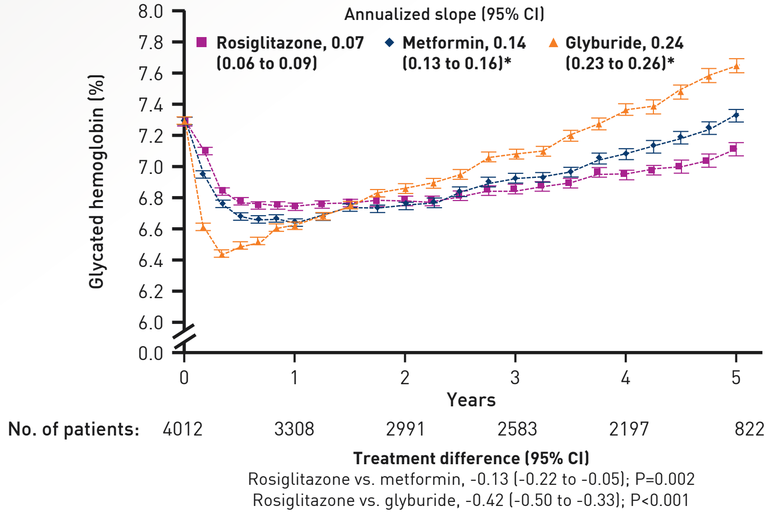
Progressive **loss of ß-cell function**, regardless of which therapy was used[3,4]

After 9 years of monotherapy, only 9% (diet), 24% (sulfonylurea), and 28% (insulin) achieve HbA_{1c} <7%[5]

Learnings from ADOPT[6]

Among newly diagnosed patients with type 2 diabetes receiving **rosiglitazone**, **metformin**, or **glyburide** as initial treatment:

Cumulative incidence of monotherapy failure using historic therapies at 5 years:



*p<0.001.

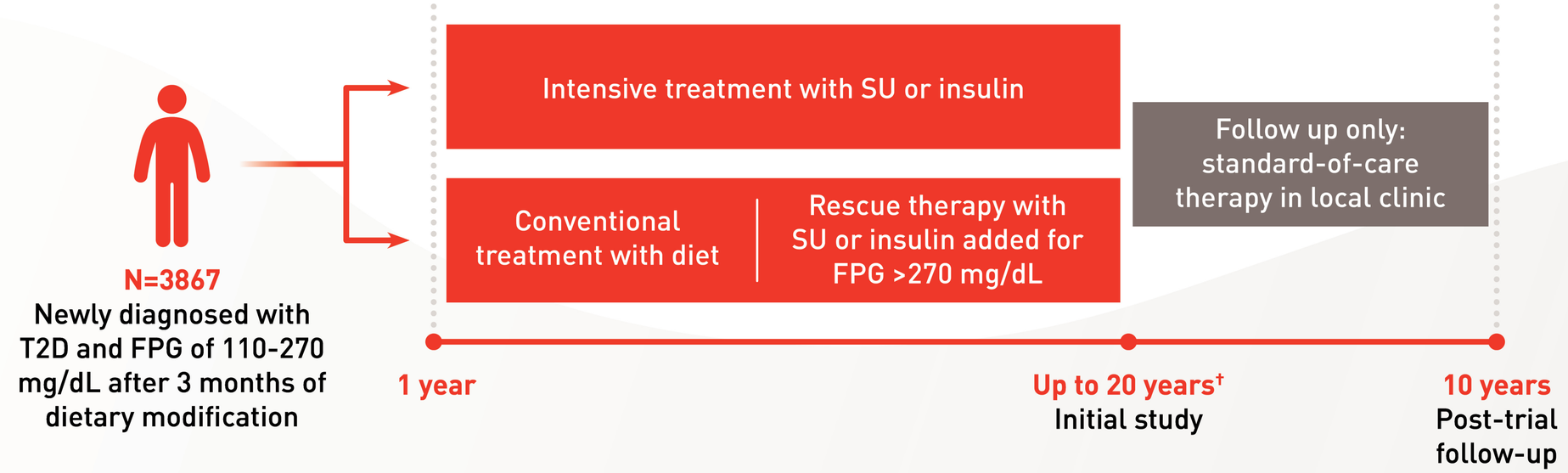
ADOPT=A Diabetes Outcome Progression Trial; UKPDS=The UK Prospective Diabetes Study.

1. DeFronzo RA. *Diabetes*. 2009;58(4):773-95. 2. UK Prospective Diabetes Study (UKPDS) Group. *The Lancet*. 1998;352(9131):837-53. 3. UK Prospective Diabetes Study Group. *Diabetes*. 1995;44(11):1249-58. 4. Matthews DR, et al. *Diabetic medicine*. 1998;15(4):297-303. 5. Turner RC, et al. *JAMA*. 1999;281(21):2005-12. 6. Kahn SE, et al. *New England Journal of Medicine*. 2006;355(23):2427-43.

Type 2 Diabetes Progression on Monotherapy

UKPDS

Effect of intensive vs. conventional glucose control on risk of micro and macrovascular complications



†The median follow-up for the sulfonylurea–insulin and metformin groups was 10.0 years and 10.7 years, respectively.
FPG=Fasting Plasma Glucose; SU=Sulfonylureas; T2D=Type 2 Diabetes; UKPDS=The UK Prospective Diabetes Study.

1. UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352(9131):837-853. 2. Holman RR, et al. *N Engl J Med.* 2008;359(15):1577-1589.

Type 2 Diabetes Progression on Monotherapy

| ADOPT |

To compare the effectiveness of rosiglitazone (TZD), as compared with glyburide (SU) and metformin, in maintaining long-term glycemic control in T2D

Note: Patients who withdraw from treatment for any reason will continue to be followed in nontreatment observational follow up.
ADOPT=A Diabetes Outcome Progression Trial; HbA_{1c}=Glycated Hemoglobin; SU=Sulfonylurea; T2D=Type 2 Diabetes; TZD=Thiazolidinedione.
Kahn SE, et al. *New England Journal of Medicine.* 2006;355(23):2427-43.

Early Combination Treatment Reduces Time to Treatment Failures[1,2]

VERIFY Trial Results

	Number of patients with good glycemic control over 5 years	Time before treatment intensification is needed	Initial treatment failure	Secondary treatment failure
Conventional stepwise therapy		62% of patients experienced treatment failure with **metformin monotherapy** during period 1		
Early combination therapy		44% of patients experienced treatment failure with **combination therapy** during period 1		

>2x

More than twice as many patients had an
extended time with good glycemic control
following early combination therapy

26%

reduction in the risk of
time to secondary treatment failure
following early combination therapy

Adapted from Matthews et al.[2]

These results indicate that long-term clinical benefits may be achieved more frequently, and potentially without additional tolerability issues, with the early initiation of medication(s) that target multiple pathways compared with traditional stepwise therapy

VERIFY=Vildagliptin Efficacy in Combination With Metformin For Early Treatment of Type 2 Diabetes.

1. Del Prato S, et al. *Diabet Med.* 2014;31(10):1178-1184. 2. Matthews D, et al. *Diabetes Ther.* 2020;11(11):2465-2476.

Early Combination Treatment Reduces Time to Treatment Failures[1,2]

Number of patients

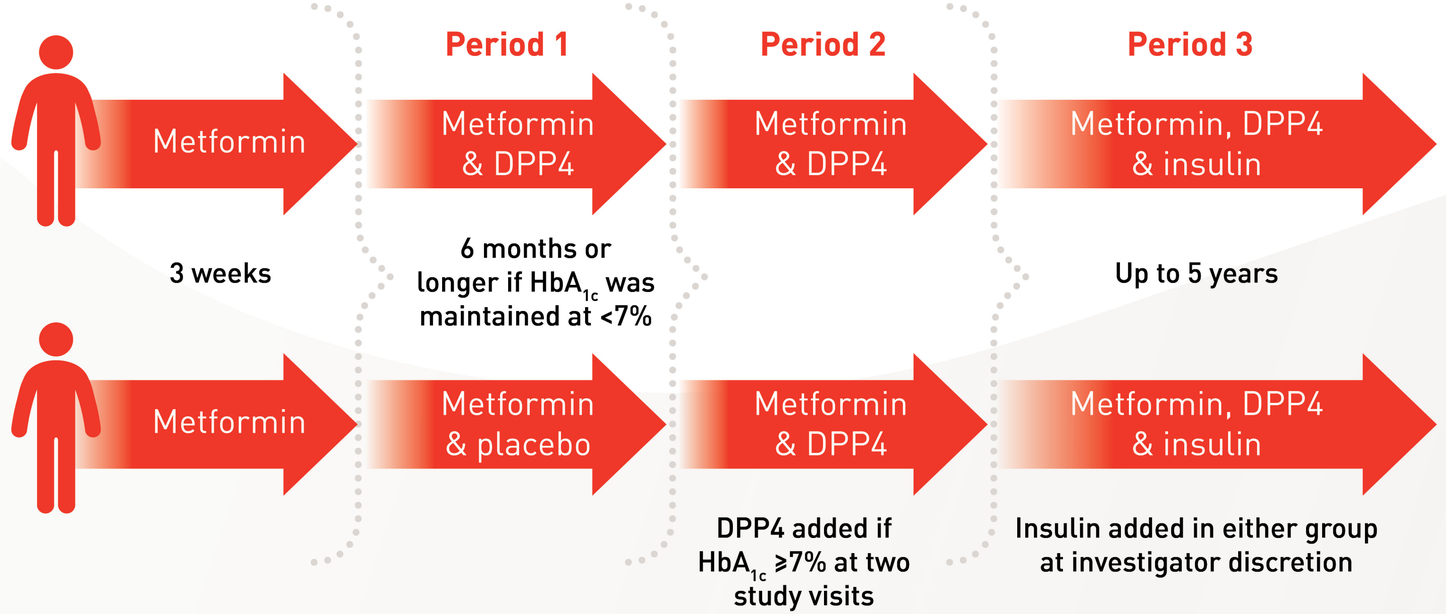
Initial

Secondary

VERIFY

To determine whether initiation of combination therapy would result in more durable glycemic control compared to metformin monotherapy in treatment-naïve patients with T2D

If HbA_{1c} was maintained at <7%, then treatment did not change



N=2001
Newly diagnosed T2D and baseline HbA_{1c} of 6.5-7.5%

DPP4=Dipeptidyl Peptidase-4 Inhibitor; HbA_{1c}=Glycated Hemoglobin; T2D=Type 2 Diabetes; VERIFY=Vildagliptin Efficacy in Combination With Metformin For Early Treatment of Type 2 Diabetes.

Matthews D et al, *Diabetes Ther*. 2020;11:2465-2476.

ADA-EASD Guidelines Recommend Incorporating Glucose-Lowering Therapies With Complementary Mechanisms of Action

Traditionally, a stepwise approach was advocated, in which a new agent is added to the existing regimen, but ***evidence is growing to support a more proactive approach*** of combining glucose-lowering agents from the time of initial diagnosis

When targets are not met, the intensification of glucose-lowering medication by combining ***agents with complementary mechanisms of action*** should be considered

Davies MJ, et al. *Diabetes Care*. 2022;45(11):2753-2786.

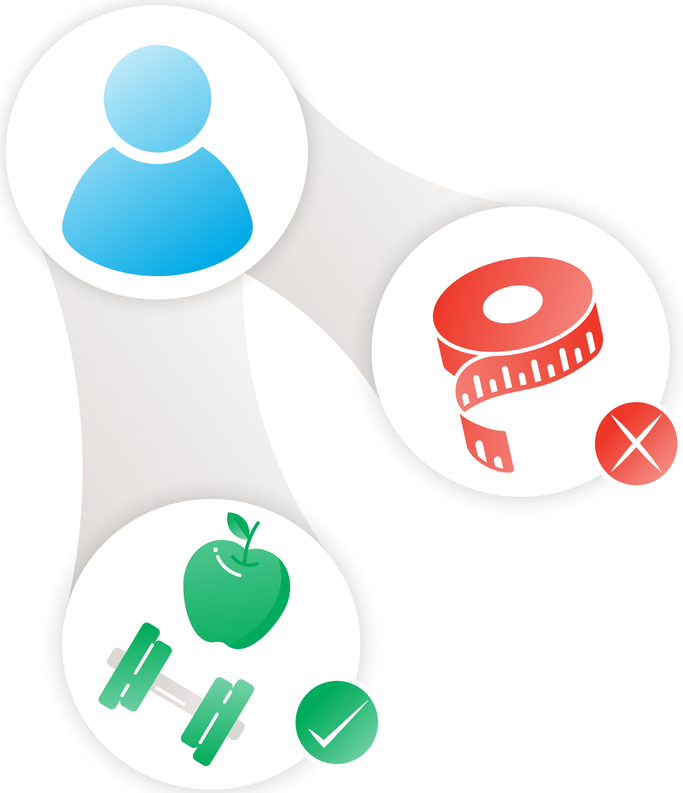
Available Medications Can Treat Multiple Metabolic Mechanisms That Drive Type 2 Diabetes Progression[1-3]

Class[2,3]	Primary Physiological Action(s)[2,3]	Core Defects[1-3]
Biguanides	▼ Hepatic glucose production	Liver
SUs	▲ Insulin secretion	Pancreatic ß-cell
TZDs	▲ Insulin sensitivity	Whole body
DPP-4 inhibitors	▲ Insulin secretion (glucose-dependent) ▼ Glucagon secretion (glucose-dependent)	Pancreatic α-cell Pancreatic ß-cell
SGLT-2 inhibitors	⊗ Blocks glucose reabsorption by the kidney, increasing glucosuria	Kidney
Incretin receptor agonists*	▲ Insulin secretion (glucose-dependent) ▼ Glucagon secretion (glucose-dependent) ▼ Delays gastric emptying ▼ Weight	Pancreatic α-cell Pancreatic ß-cell GI tract

*Only actions consistent in both classes of incretin receptor agonists shown; the GIP/GLP-1 RA class acts on additional defects.
Schematic is intended to provide an overview of T2D drugs and is not specific to only one product within each class listed. It is not limited to make any express or implied comparison among products. Classes shown are from the ADA guidelines and do not represent all T2D classes available to treat hyperglycemia.
DPP-4=Dipeptidyl Peptidase-4; GIP=Glucose-Dependent Insulinotropic Polypeptide; GLP-1RA=Glucagon-Like Peptide-1 Receptor Agonist; SGLT2=Sodium-Glucose Cotransporter-2; SU=Sulfonylurea; TZD=Thiazolidinedione.
1. DeFronzo RA. *Diabetes*. 2009;58(4):773-795. 2. Inzucchi SE, et al. *Diabetes Care*. 2015;38:140-149. 3. Mounjaro (tirzepatide once weekly) [Summary of Product Characteristics]. Houten, Utrecht, Netherlands: Eli Lilly and Company.

Visit 5 - She returns in 4 months *(20 months after diagnosis)*

- She is very pleased with her progress in lifestyle modifications, including improving her diet and exercising.
- Her HbA_{1c} remains at 7.4% and she is very frustrated by the lack of weight change despite lifestyle changes.
- She is still somewhat reluctant to try additional therapy, though.



Decision Point 3: In addition to continuing metformin 1500 mg daily, which of the following may be the next best step?

A Start an SGLT-2 inhibitor

B Have her meet with an exercise physiologist

C Start an incretin receptor agonist with high glycemic efficacy and weight reduction

SGLT-2=Sodium-Glucose Cotransporter-2.

Decision Point 3: In addition to continuing metformin 1500 mg daily, which of the following may be the next best step?

A Start an SGLT-2 inhibitor

B Have her meet with an exercise physiologist

Incorrect – there may be a better option for this patient. Starting an SGLT-2 inhibitor is a reasonable consideration, especially given that she has room for improvement in her glycemic control. However, according to the ADA/EASD Consensus Report, a regimen with high to very high dual glucose and weight efficacy is recommended in individuals needing to achieve glycemic and weight management goals.

ADA=American Diabetes Association; EASD=European Association for the Study of Diabetes; SGLT-2=Sodium-Glucose Cotransporter-2.

Davies MJ, et al. *Diabetes Care*. 2022;45(11):2753-2786.

SGLT-2=Sodium-Glucose Cotransporter-2.
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Decision Point 3: In addition to continuing metformin 1500 mg daily, which of the following may be the next best step?

A Start an SGLT-2 inhibitor

B Have her meet with an exercise physiologist

Incorrect – there may be a better option for this patient. Lifestyle counseling and modifications, including physical activity, are critically important. However, considering that biologic contributors of obesity and high HbA_{1c} are often difficult to overcome with lifestyle modifications alone, it is important to remember that pharmacotherapy is often also needed to help get patients to glycemic and weight targets. Early weight loss is associated with delayed disease progression, and incorporating a glucose-lowering therapy with high efficacy for weight loss may improve long-term outcomes.

Davies MJ, et al. *Diabetes Care.* 2022;45(11):2753-2786.

SGLT-2=Sodium-Glucose Cotransporter-2.

Decision Point 3: In addition to continuing metformin 1500 mg daily, which of the following may be the next best step?

A Start an SGLT-2 inhibitor

B Have her meet with an exercise physiologist

Correct – this may be an appropriate option for this patient.

According to the ADA/EASD Consensus Report, incretin receptor agonists have high to very high efficacy for glycemic control and intermediate to very high efficacy for weight reduction.

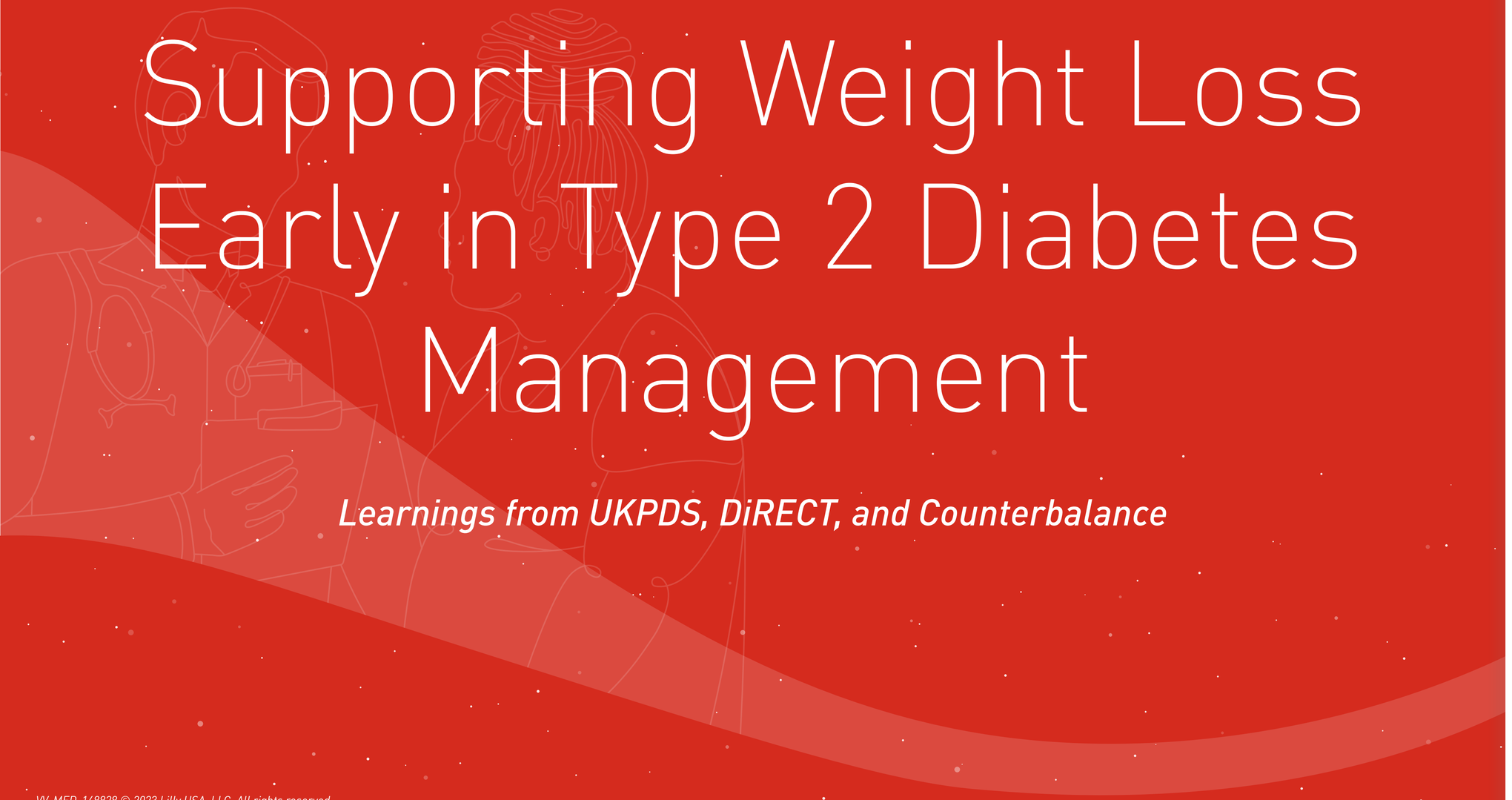
ADA=American Diabetes Association; EASD=European Association for the Study of Diabetes.

Davies MJ, et al. *Diabetes Care.* 2022;45(11):2753-2786.

SGLT-2=Sodium-Glucose Cotransporter-2.

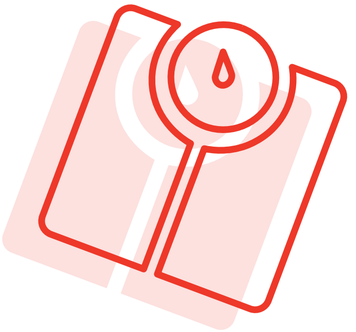
Supporting Weight Loss Early in Type 2 Diabetes Management

Learnings from UKPDS, DiRECT, and Counterbalance



ADA-EASD Guidelines on Achievement of Weight Goals for Type 2 Diabetes Management[1,2]

> ***Weight loss of 5%-10%*** confers metabolic improvement; weight loss of ***10%-15%*** or more may have a disease-modifying effect[2]



> Weight loss may exert benefits that extend ***beyond glycemic management*** to improve risk factors for cardiometabolic disease[2]

1. American Diabetes Association. *Diabetes Care*. 2022;45(suppl 1):S83-S96. 2. Davies MJ, et al. *Diabetes Care*. 2022;45(11):2753-2786.

Excess Weight and Glycemic Control

UKPDS

UKPDS demonstrated that fasting plasma glucose and HbA_{1c} increase progressively to a greater extent in participants with obesity compared to those without obesity.[1]

DiRECT

The DiRECT trial demonstrated that early weight reduction is associated with improved HbA_{1c} levels and participants achieving ≥15 kg weight loss were more likely to achieve HbA_{1c} <6.5%.[2]

COUNTERBALANCE

The Counterbalance study is a small study that demonstrated improvement in glycemic control following weight loss was greater in those with shorter duration of T2D than in those with longer duration of T2D.[3]

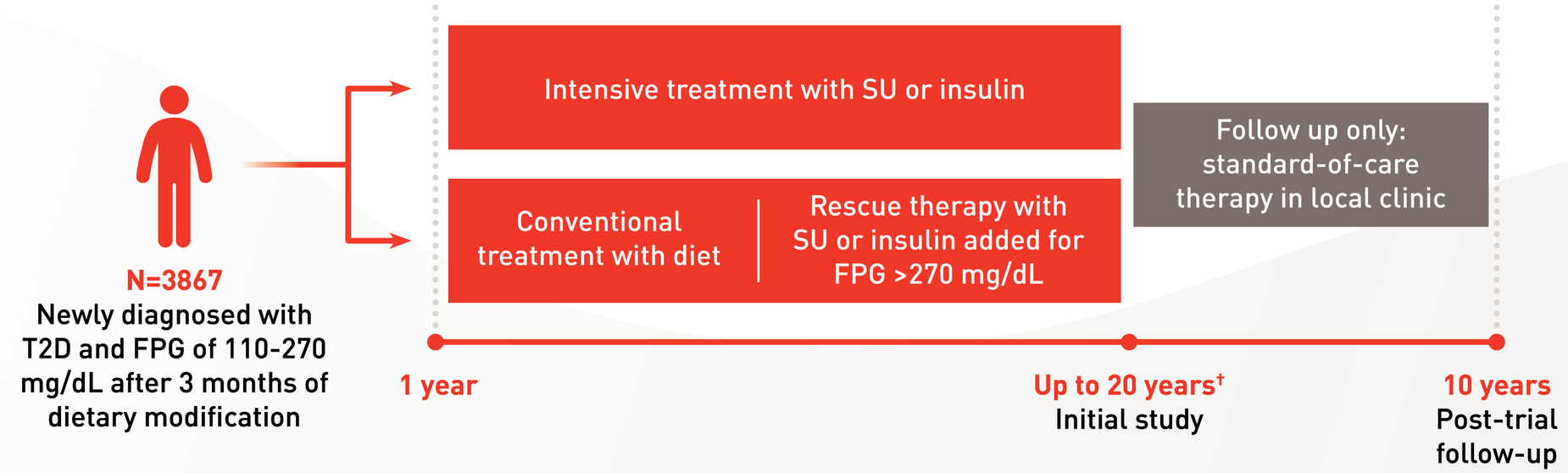
Counterbalance=Counteracting Beta Cell Failure By Long Term Action to Normalize Calorie Intake; DiRECT=Diabetes Remission Clinical Trial; UKPDS=The UK Prospective Diabetes Study.

1. United Kingdom Prospective Diabetes Study Group. *BMJ: British Medical Journal.* 1995:83-8. 2. Lean MEJ, et al. *Lancet Diabetes Endocrinol.* 2019;7(5):344-355. 3. Steven S et al. *Diabetes Care.* 2016;39:808-815.

Excess Weight and Glycemic Control

UKPDS

Effect of intensive vs. conventional glucose control on risk of micro and macrovascular complications



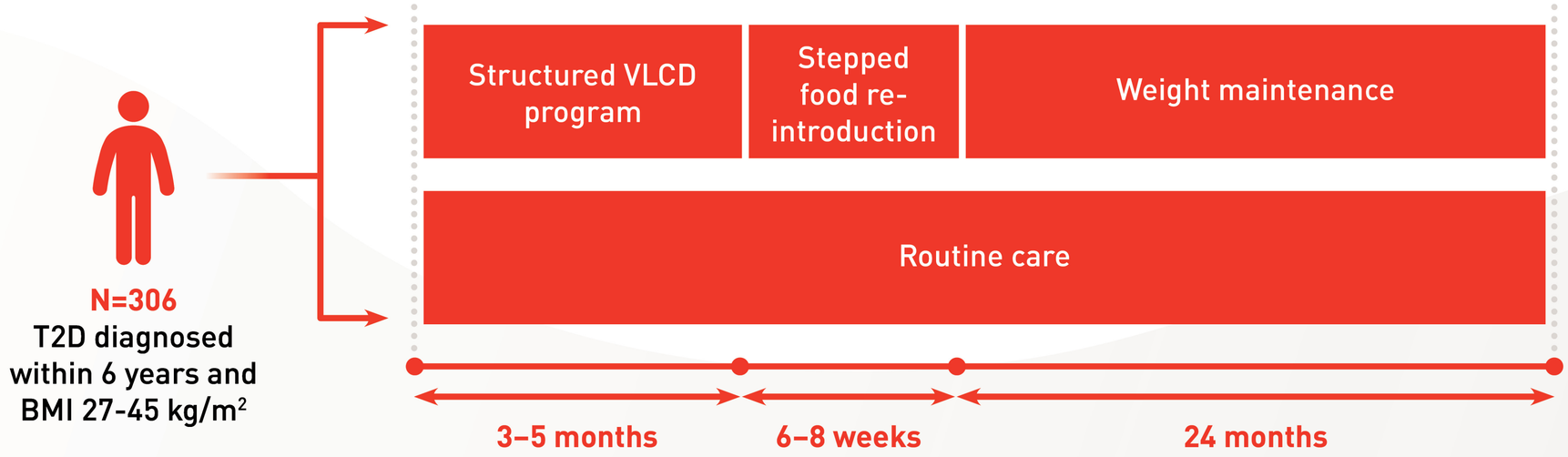
†The median follow-up for the sulfonylurea–insulin and metformin groups was 10.0 years and 10.7 years, respectively.
FPG=Fasting Plasma Glucose; SU=Sulfonylureas; T2D=Type 2 Diabetes; UKPDS=The UK Prospective Diabetes Study.

1. UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352(9131):837-853. 2. Holman RR, et al. *N Engl J Med*. 2008;359(15):1577-1589.

Excess Weight and Glycemic Control

DiRECT

Effect of weight loss on T2D remission

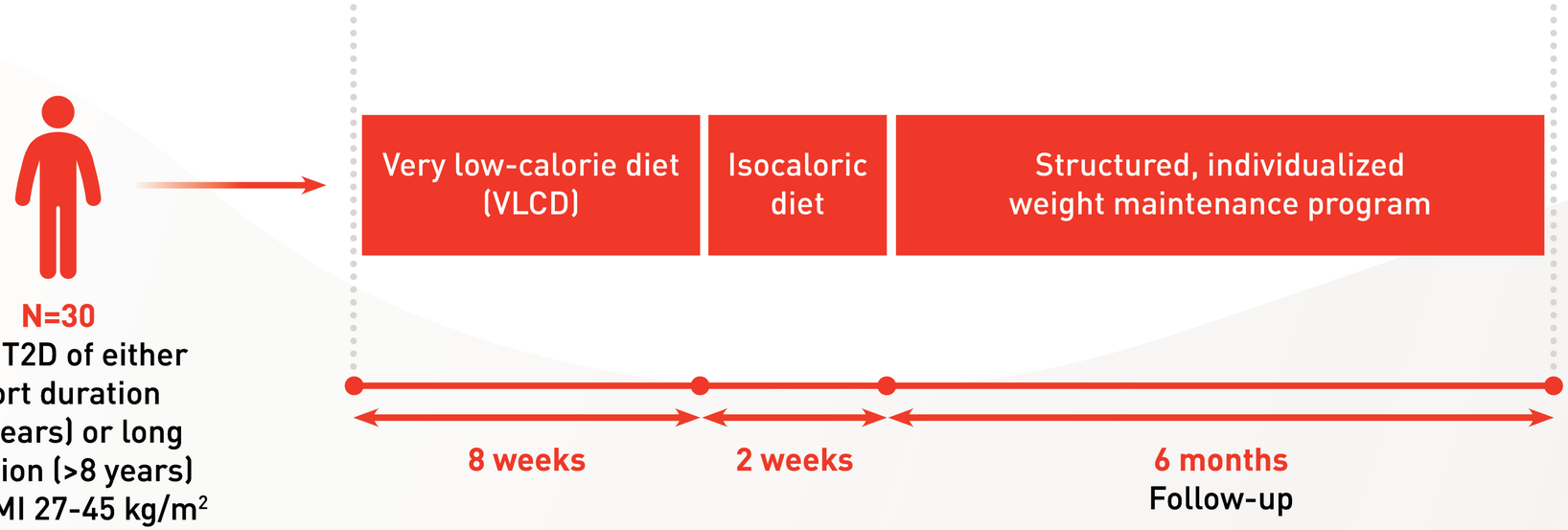


BMI=Body Mass Index; DiRECT=Diabetes Remission Clinical Trial; T2D=Type 2 Diabetes; VLCD=Very Low-Calorie Diet.

Lean MEJ et al. *Lancet Diabetes Endocrinol.* 2019;7(5):344-355.

Counterbalance

To study the effect of weight loss, achieved through a VLCD, on control of fasting plasma glucose levels in T2D



BMI=Body Mass Index; Counterbalance=Counteracting Beta Cell Failure By Long Term Action to Normalize Calorie Intake; T2D=Type 2 Diabetes; VLCD=Very Low-Calorie Diet.

Steven S et al. *Diabetes Care.* 2016;39:808-815.

CLINIC-*Sim*

Simulating a Patient-Centered Approach to Optimize Early Glycemic Control and Weight Management in Type 2 Diabetes