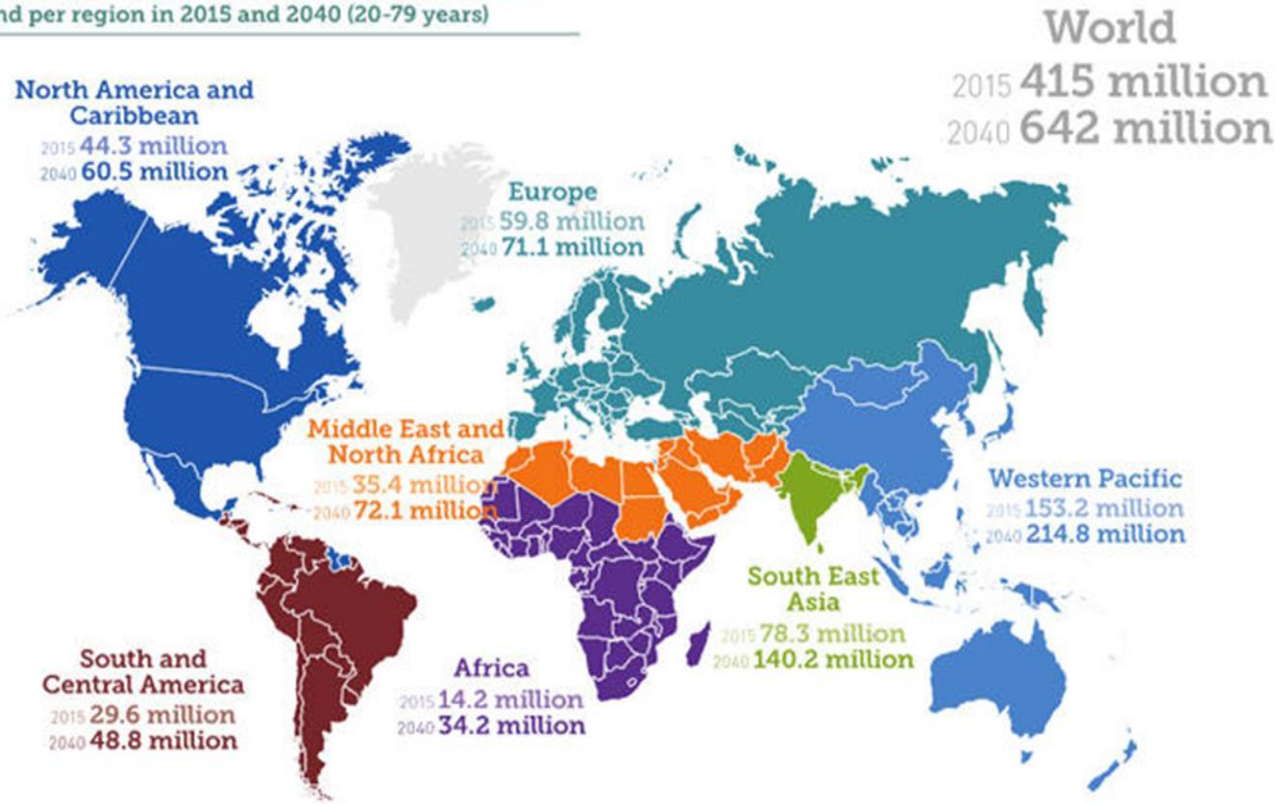
Early Insulinisattion

Esfahanian F., MD, Endocrinologist
TUMS

99/4/20

Estimated number of people with diabetes worldwide and per region in 2015 and 2040 (20-79 years)



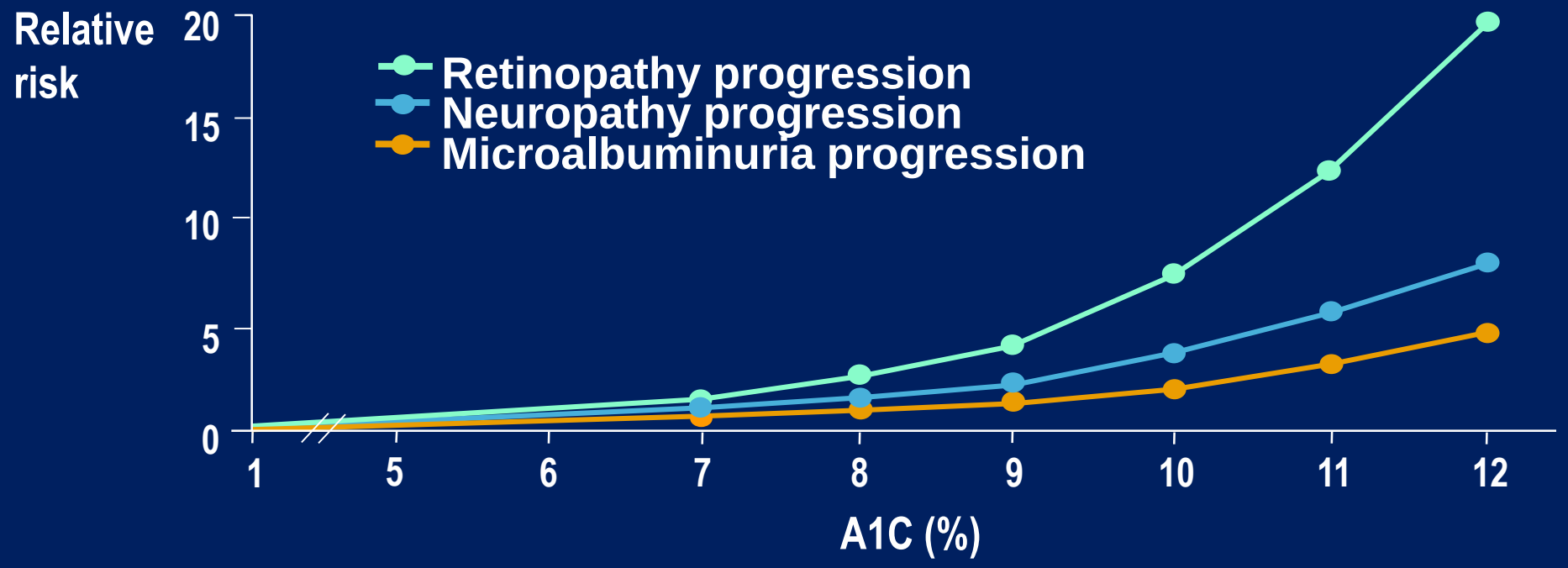
Glycemic control is fundamental to the management of diabetes

- Long-term challenges:
  - Prevent long-term deterioration of glucose homeostasis
  - Prevent microvascular complications
  - Prevent macrovascular complications
  - Quality of life

American Diabetes Association. Diabetes Care. 2012;35(suppl 1):S11-S61

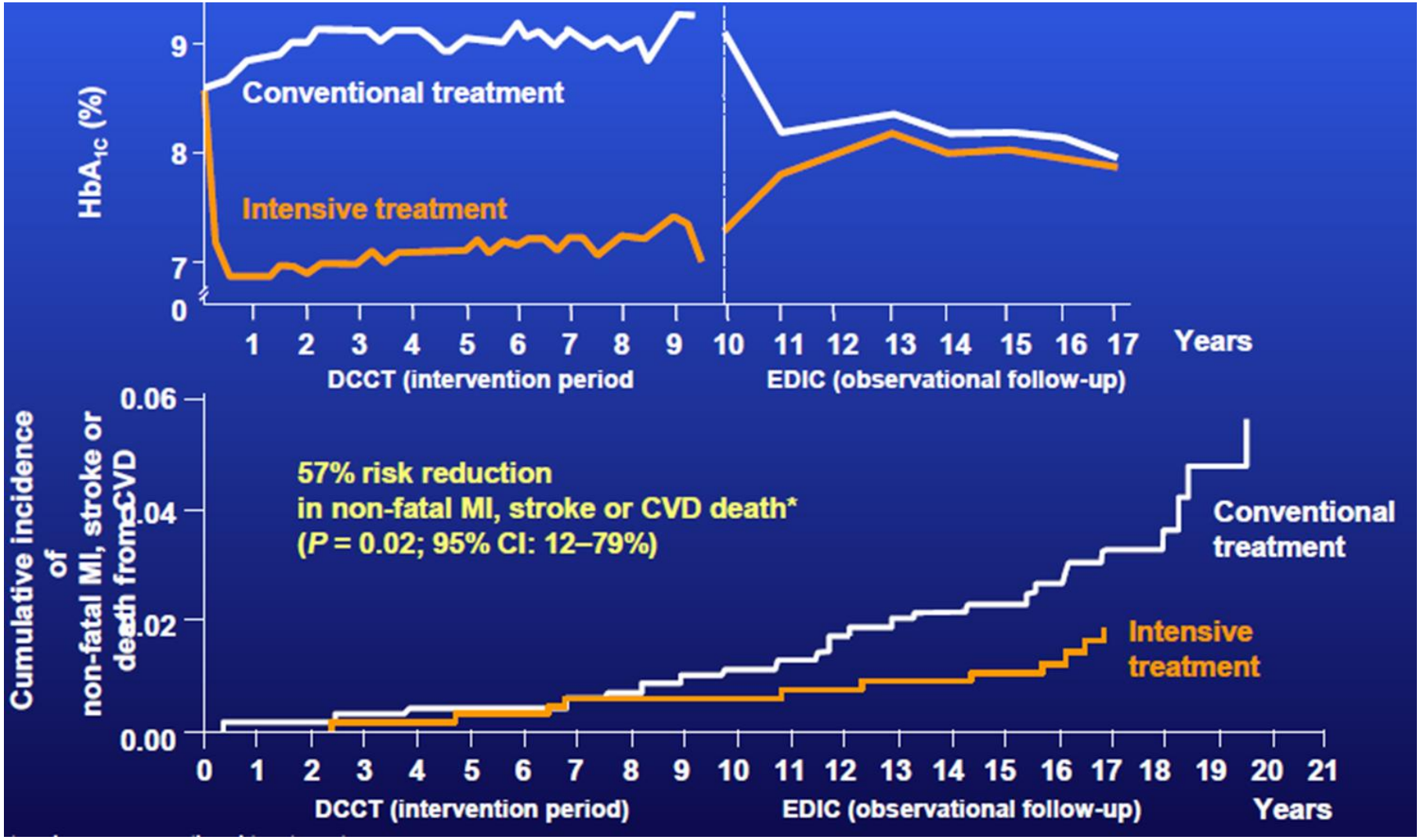
Risk of Microvascular Complications *vs.* A1C in Type 1 Diabetes

Results From the DCCT



Skyler JS. Endocrinol Metab Clin North Am. 1996;25:243-254

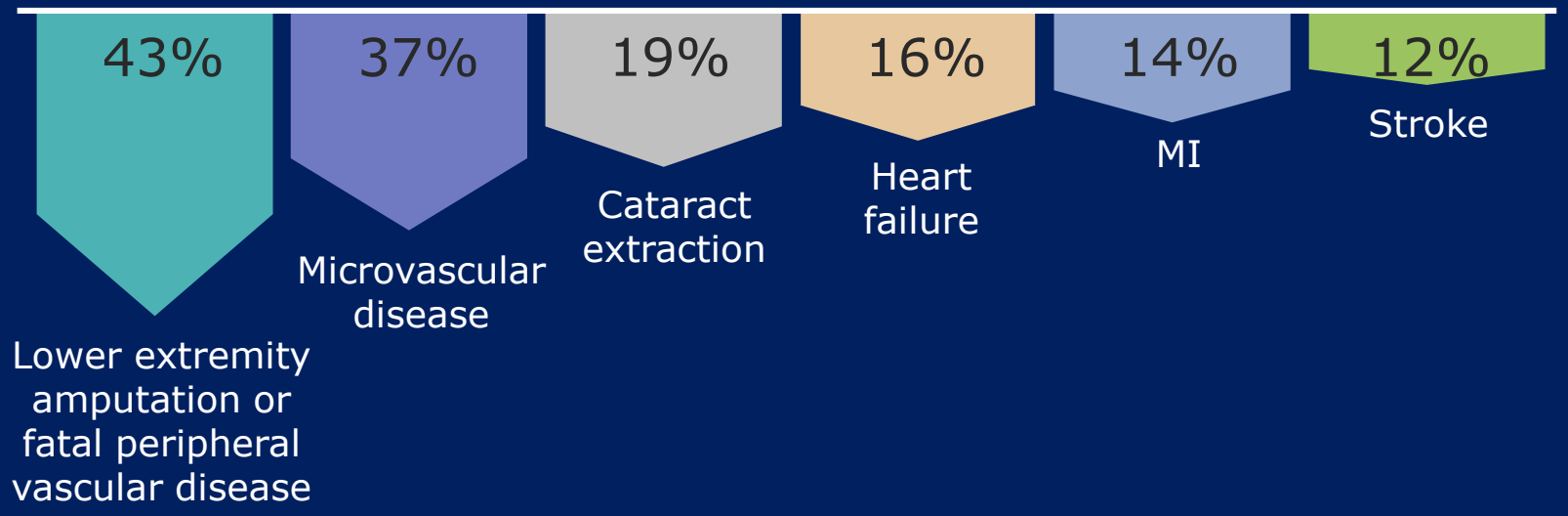
DCCT/EDIC: glycemic control reduces the risk of nonfatal MI, stroke or death from CVD in type 1 diabetes



Adapted from DCCT. N Engl J Med 1993; 329:977–986. DCCT/EDIC. JAMA 2002; 287:2563–2569. DCCT/EDIC. N Engl J Med 2005; 353:2643–2653.

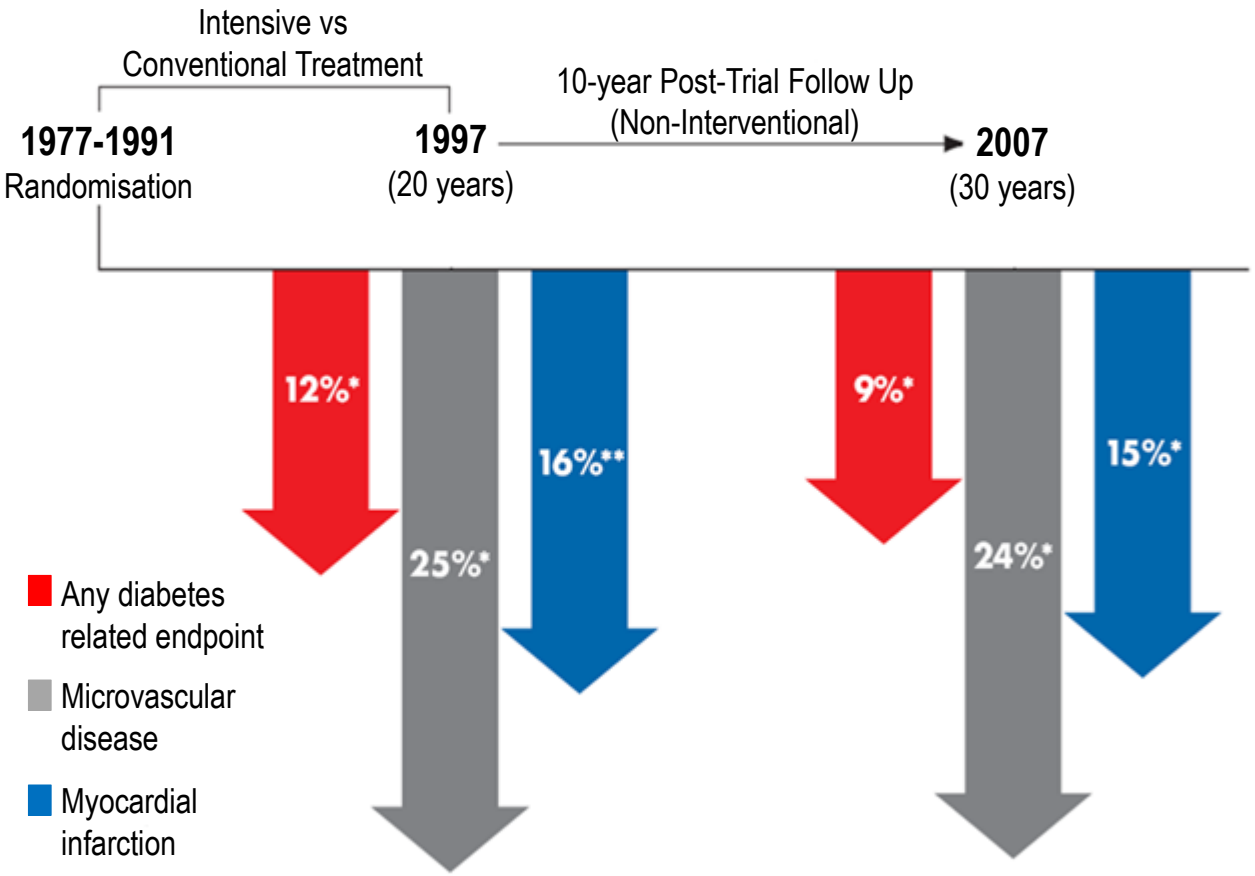
Improving control reduces risks of long-term complications

- Every 1% drop in HbA_{1c} can reduce long-term diabetes complications



UKPDS: Stratton et al. BMJ 2000;32:405–12

Improvements in glycaemic control reduces the risk of complications in T2D

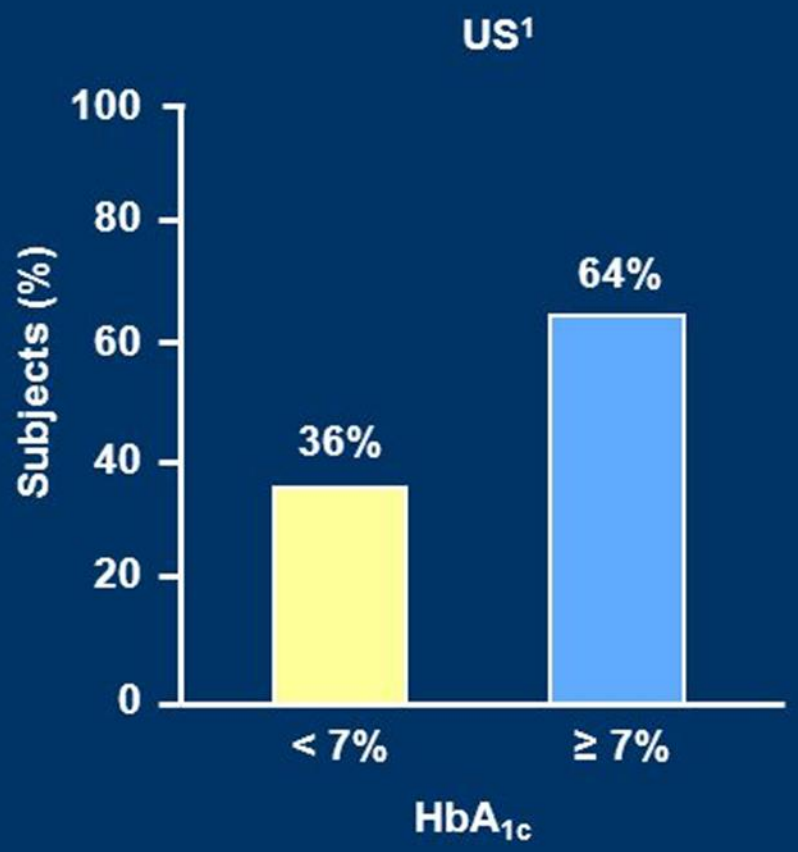


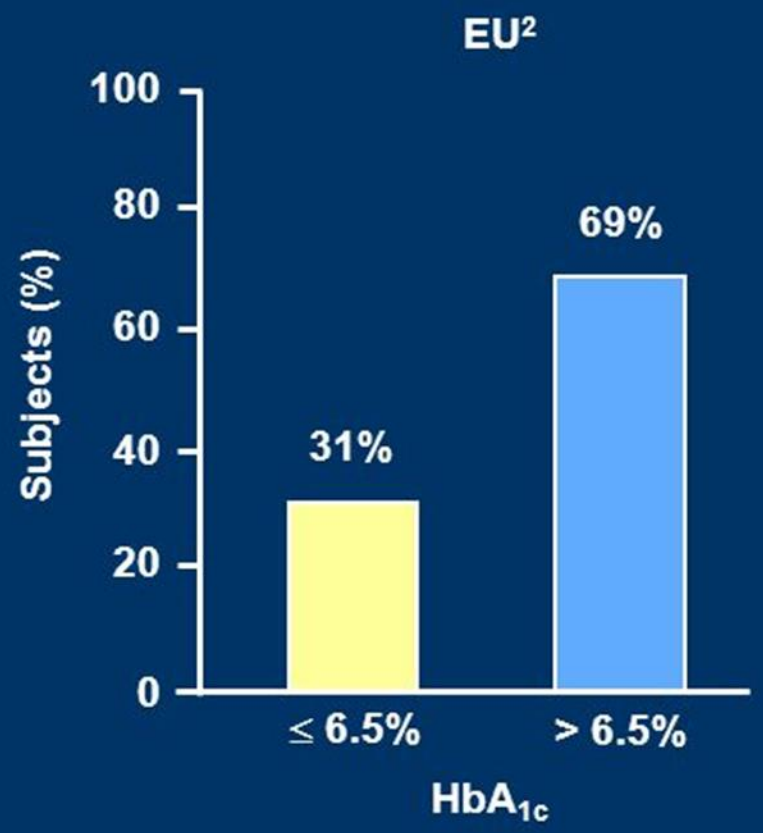
[* p<0.05 ** p=0.052] – Intensive vs Conventional Treatment

The benefits and risks in the UKPDS
T2D, type 2 diabetes

Holman *et al. N Engl J Med* 2008;359:1577–89; UKPDS Study Group. *Lancet* 1998;352:837–53

Majority of type 2 diabetes patients are not at HbA_{1c} goal





[1]Koro CE, *et al*. *Diabetes Care* 2004; 27:17–20.
[2]Liebl A. *Diabetologia* 2002; 45:S23–S28.

Care Delivery Systems.

- 33-49% of patients still do not meet targets for A1C, blood pressure, or lipids
- Only14% of patients meet targets for all A1C, BP, lipids, and nonsmoking status
- Progress in CVD risk factor control is slowing
- System-level improvements are needed

ADA guideline 2020

American Diabetes Association.
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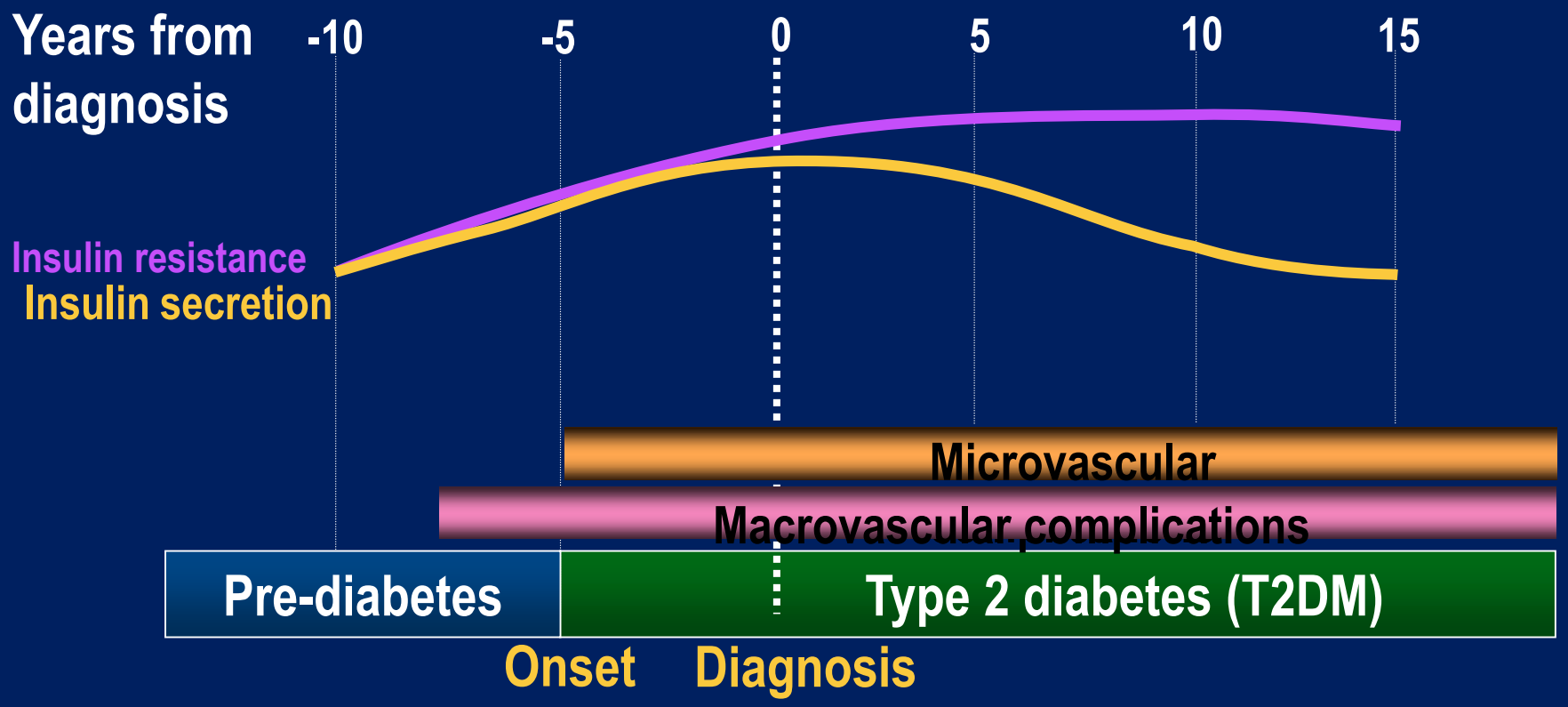
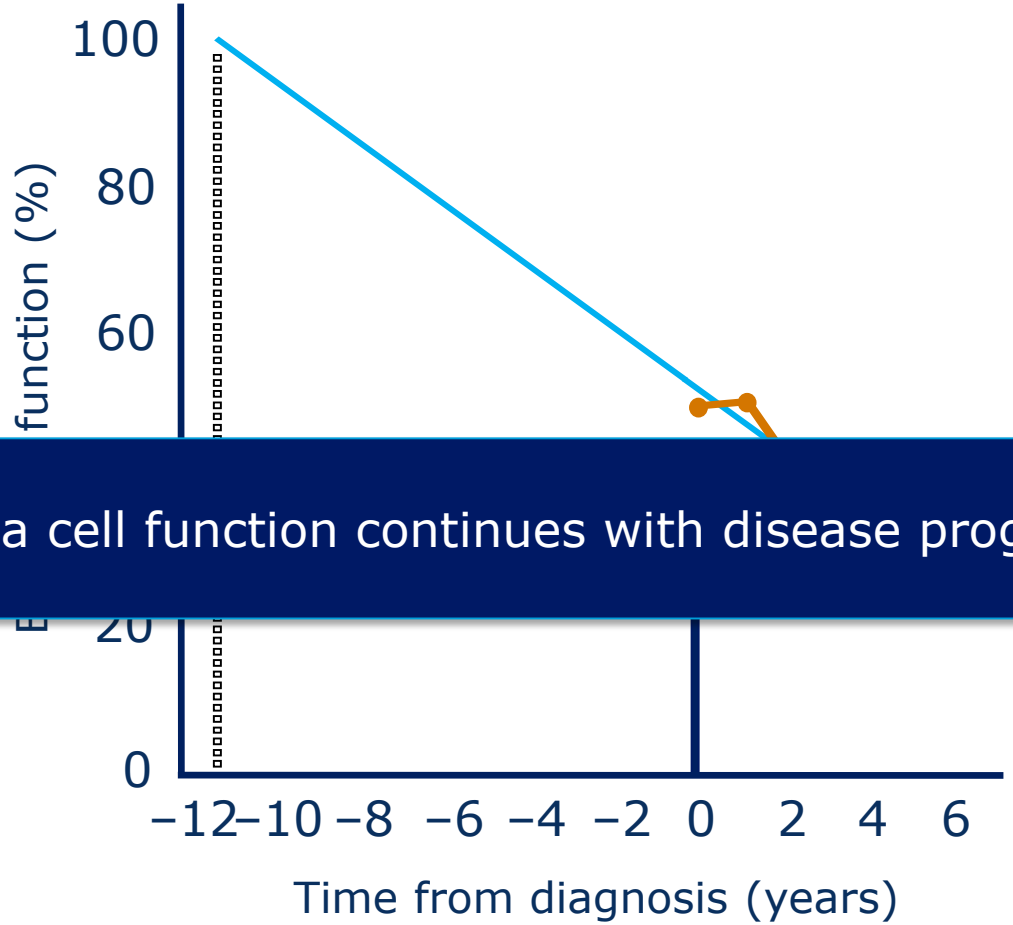
Natural History of Type 2 Diabetes Progression



Progressive loss of beta-cell function



Loss of beta cell function continues with disease progression

UKPDS, UK Prospective Diabetes Study

Holman. *Diabetes Res Clin Pract* 1998;40(Suppl.):S21–5

Progressive beta cell damage

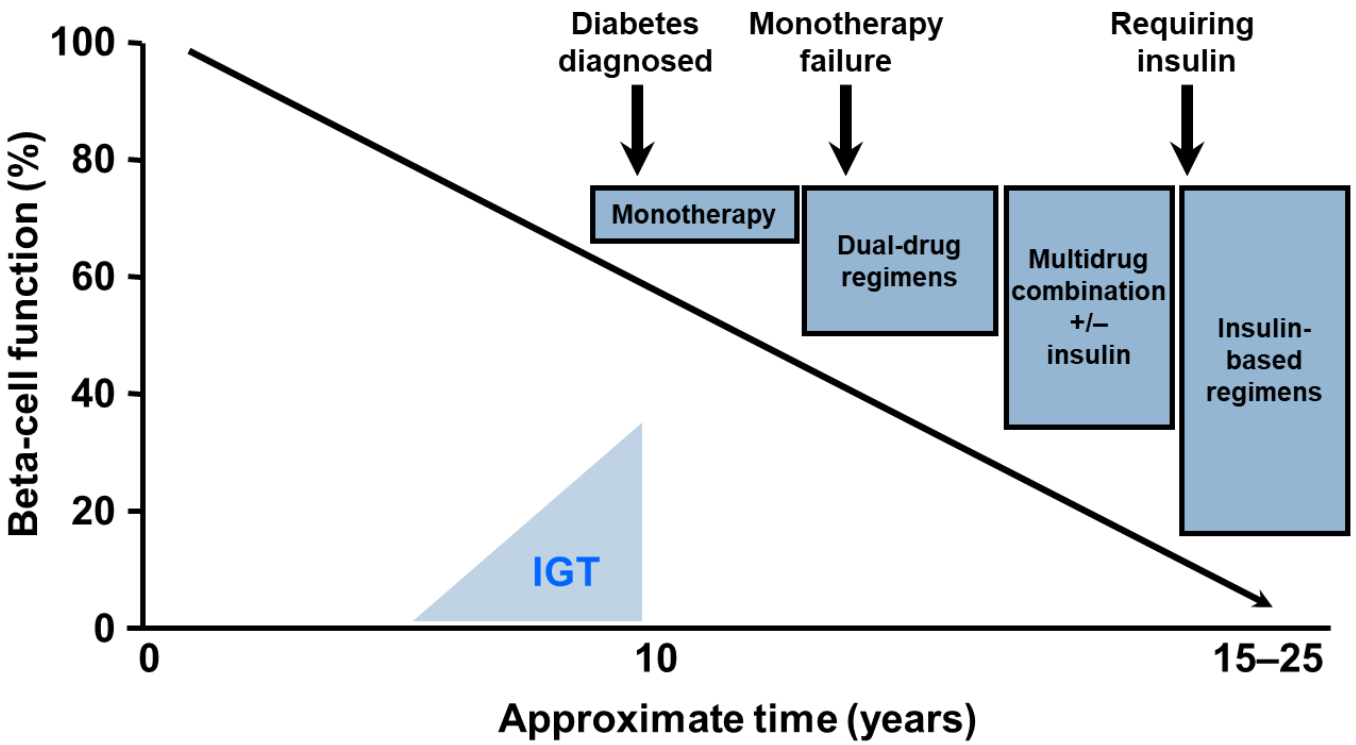
- **Type 2 diabetes is a progressive disease**

- **After 3 years of monotherapy with insulin, a sulfonylurea, or metformin, approximately *50%* of patients in the UKPDS required combination therapy;**
  - **by 9 years, this percentage had increased to *75%***

- **In the UK Prospective Diabetes Study, 9 years after diagnosis almost 80% of patients on oral agents required insulin supplementation**

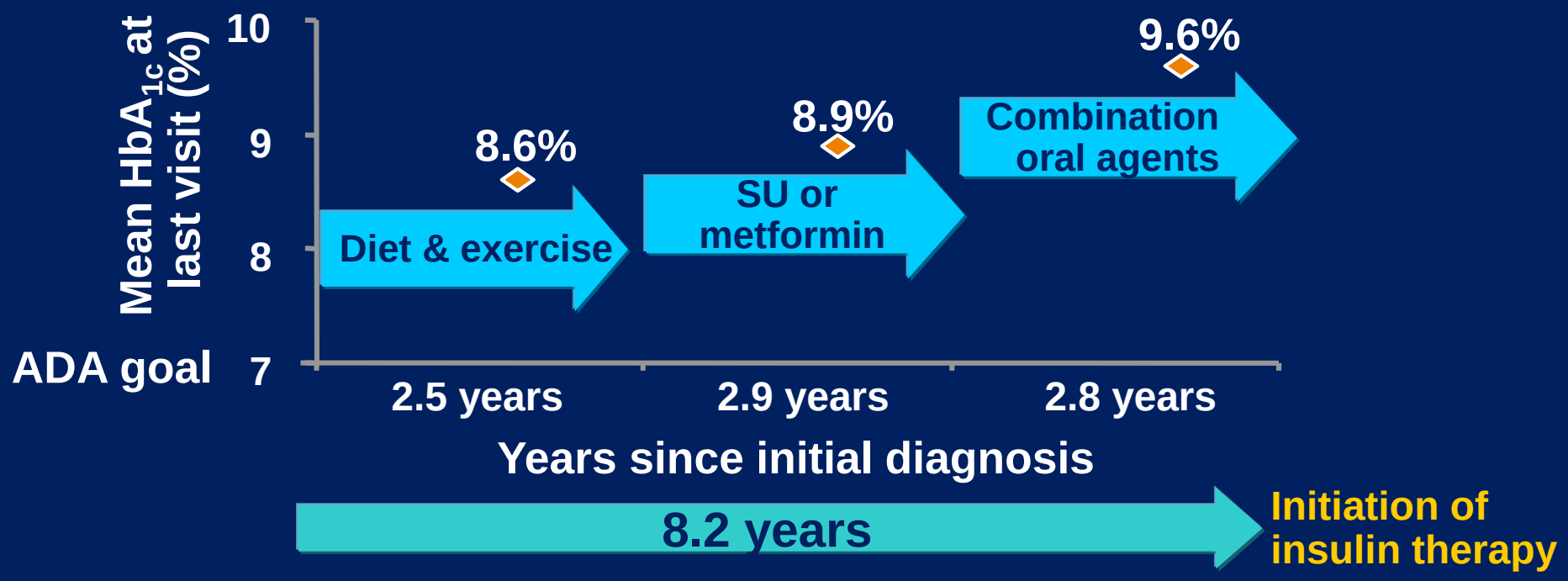
JAMA 1999; 281:2005–2012

The Number of Medications Taken Usually Increases With Duration of Disease



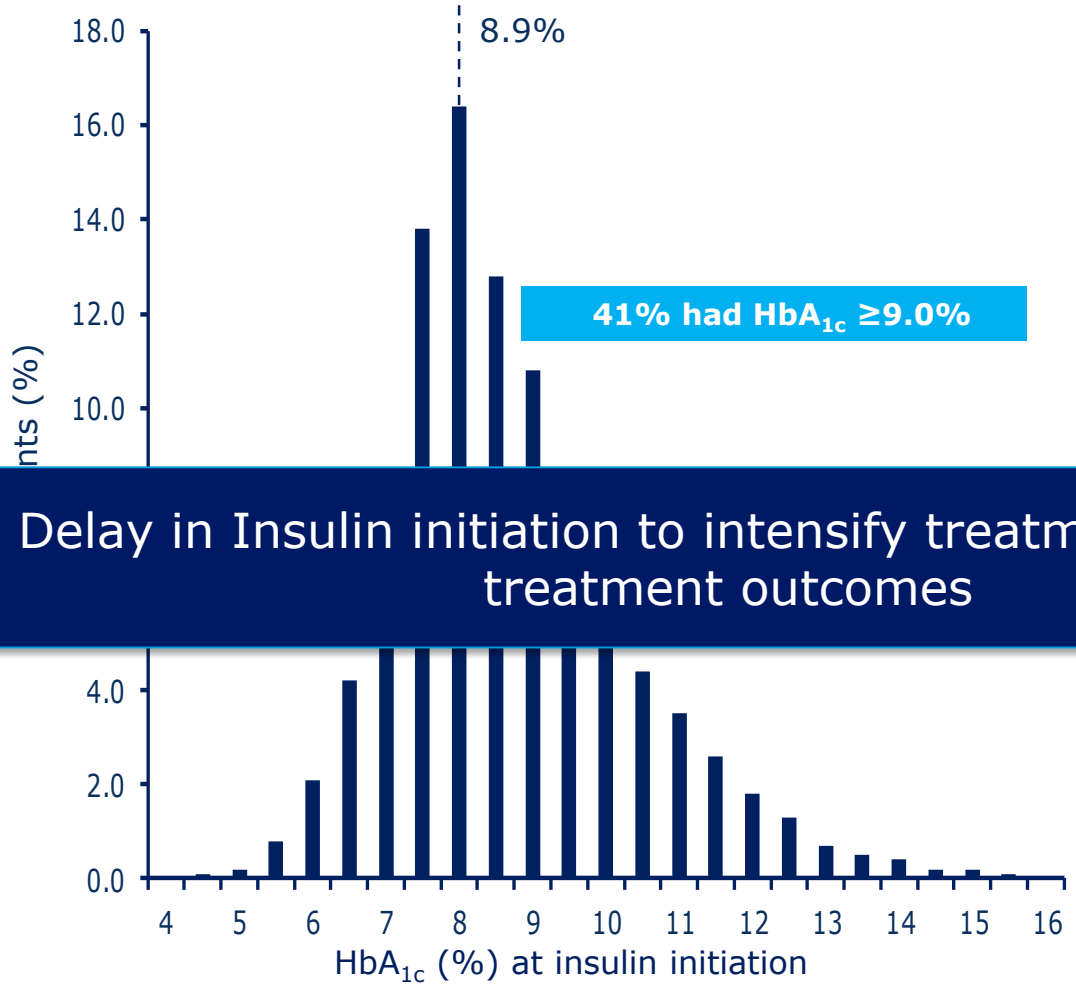
IGT=impaired glucose tolerance.
UKPDS 16. *Diabetes*. 1995;44:1249–1258.
Turner RC et al. *JAMA*. 1999;281:2005–2012; Warren RE. *Diabetes Res Clin Pract*. 2004;65:S3–S8; Lebovitz HE. *Med Clin N Am*. 2004;88:847–863.

Clinical inertia: 'failure to advance therapy when recommended'



Chan JC, et al. Diabetes Care 2009;32:227–33

Patients remain on multiple OAD therapy too long



Clinical inertia exists despite:

- The benefits of timely glycaemic control
- Guidelines encouraging earlier use of insulin

At insulin initiation in SOLVE:

- Average HbA_{1c} was 8.9%

Delay in Insulin initiation to intensify treatment may affect treatment outcomes

OAD, oral antidiabetic drug

Khunti *et al. Diabetes Obes Metab* 2012;14:654–61

Multinational, observational study of T2DM (66,726) ACHIEVE study: Insulin therapy started in routine clinical care when HbA_{1c} 9.3–9.8%

	China	S. Asia	E. Asia	N. Africa	Mid East	Lat. Am.	Russia
n	9,493	21,107	9,062	3,623	11,971	1,032	2,954
Age (yrs)	55.7	51.7	56.5	58.3	52.8	59.6	59.2
T2DM (yrs)	7.9	6.7	12.5	11.4	10.2	15.5	9.6
Complications (%)	86.1	94.0	90.3	89.7	79.9	90.7	96.1
CV disease (%)	22.9	32.5	29.4	28.5	30.5	35.3	74.6
Renal disease (%)	26.1	28.7	34.6	36.5	43.6	41.8	41.7
Eye problems (%)	25.6	22.0	29.9	41.2	36.8	41.2	71.0
Foot ulcer (%)	2.5	6.5	5.8	3.5	8.7	7.7	5.1
Neuropathy (%)	33.7	29.4	40.1	38.9	56.0	47.6	84.4

Complications already present in people with T2DM when initiating insulin therapy

Consequences of Clinical inertia

For every 20 people with type 2 diabetes with an HbA1c value 1% above the 7% target, one will suffer a microvascular complication within 5 years.

A low-density lipoprotein (LDL) cholesterol level 30 mg/dl above goal will result in a myocardial infarction or stroke, and for every 20 patients with a blood pressure 10 mmHg above target, one will suffer a myocardial infarction or stroke and one will progress their microvascular disease within the same 5-year period.

Key Recommendations

- Treatment decisions **should be timely** and based on evidence-based guidelines that are tailored to patient preferences, prognoses, and comorbidities.

- Providers should consider the burden of treatment and self-efficacy of patients when recommending treatments.

American Diabetes Association Standards of Medical Care in Diabetes.
Promoting Health and Reducing Disparities in Populations. Diabetes Care 2017; 40 (Suppl. 1): S6-S10

American Diabetes Association Diabetes Care Volume 41, Supplement 1, January 2018

Antihyperglycemic Therapy in Adults with Type 2 Diabetes

At diagnosis, initiate lifestyle management, set A1C target, and initiate pharmacologic therapy based on A1C:

A1C is less than 9%, **consider Monotherapy.**

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy — Lifestyle Management + Metformin

Initiate metformin therapy if no contraindications* (See Table 8.1)

A1C at target after 3 months of monotherapy?

Yes: - Monitor A1C every 3–6 months

No: - Assess medication-taking behavior
- Consider Dual Therapy

Dual Therapy — Lifestyle Management + Metformin + Additional Agent

Dual Therapy Lifestyle Management + Metformin + Additional Agent

ASCVD?

Yes: – Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with * on p. S75 and **Table 8.1**)

No: – Add second agent after consideration of drug-specific effects and patient factors (See Table 8.1)

A1C at target after 3 months of dual therapy?

Yes: - Monitor A1C every 3–6 months

No: - Assess medication-taking behavior
- Consider Triple Therapy

Triple Therapy Lifestyle Management + Metformin + Two Additional Agents

Add third agent based on drug-specific effects and patient factors# (See Table 8.1)

A1C at target after 3 months of triple therapy?

Yes: - Monitor A1C every 3–6 months

No: - Assess medication-taking behavior
- Consider Combination Injectable Therapy (See Figure 8.2)

Combination Injectable Therapy (See Figure 8.2)

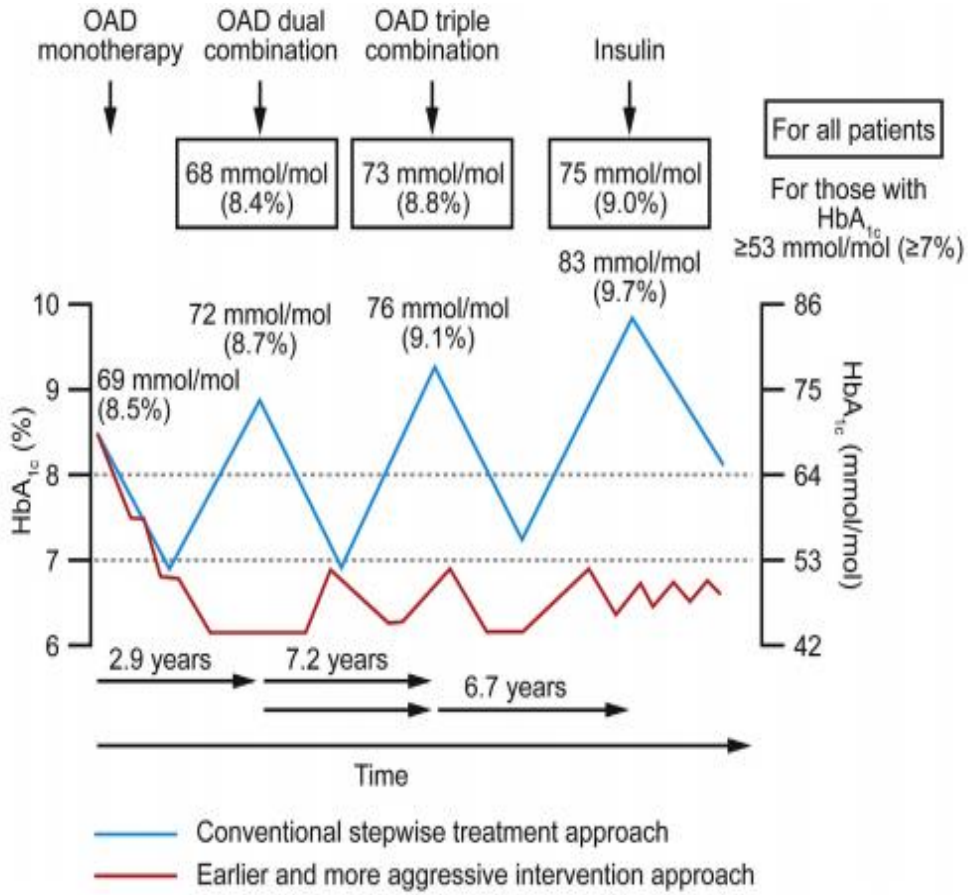


Fig. 2 – Median time to intensification and mean HbA_{1c} at intensification in patients with type 2 diabetes currently treated with one or two OADs with intensification to two OADs or insulin, respectively.

OAD, oral antidiabetic drug.

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Glycemic Recommendations for Nonpregnant Adults with Diabetes

A1C	**<7.0%* (<53 mmol/mol)**
Preprandial capillary plasma glucose	**80–130 mg/dL* (4.4–7.2 mmol/L)**
Peak postprandial capillary plasma glucose†	**<180 mg/dL* (<10.0 mmol/L)**

* Goals should be individualized.
† Postprandial glucose measurements should be made 1–2 hours after the beginning of the meal.

American Diabetes Association Standards of Medical Care in Diabetes.
Glycemic targets. Diabetes Care 2017; 40 (Suppl. 1): S48-S56

Table 6.3—Summary of glycemic recommendations for many nonpregnant adults with diabetes

A1C	<7.0% (53 mmol/mol)*
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (10.0 mmol/L)

*More or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations. †Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.

Glycemic Targets:
Standards of Medical Care in Diabetes - 2020. Diabetes Care 2020;43(Suppl. 1): S66-S76

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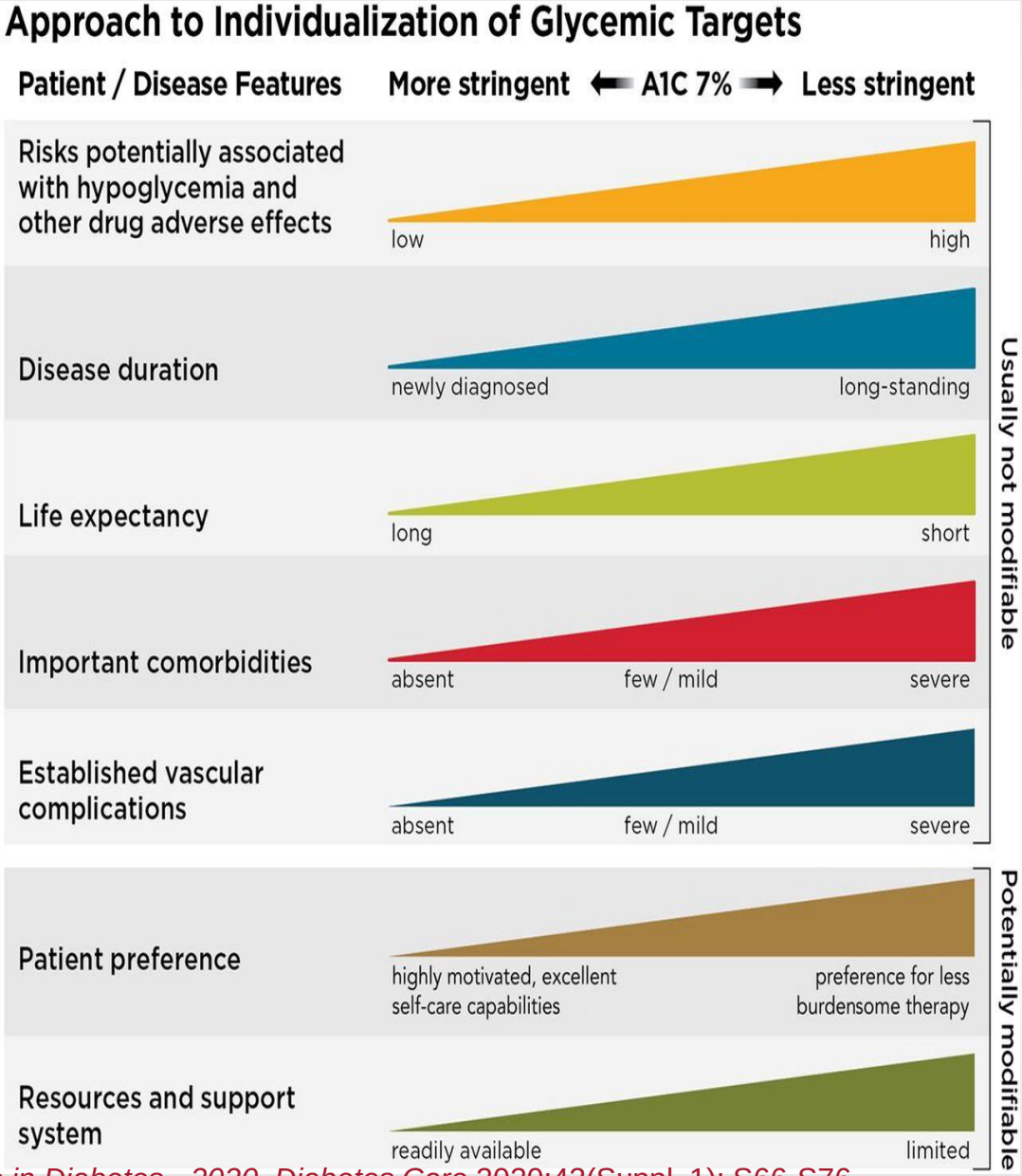

Glycemic Targets:
Standards of Medical Care in Diabetes - 2020. Diabetes Care 2020;43(Suppl. 1): S66-S76

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Diabetes is a dynamic disease

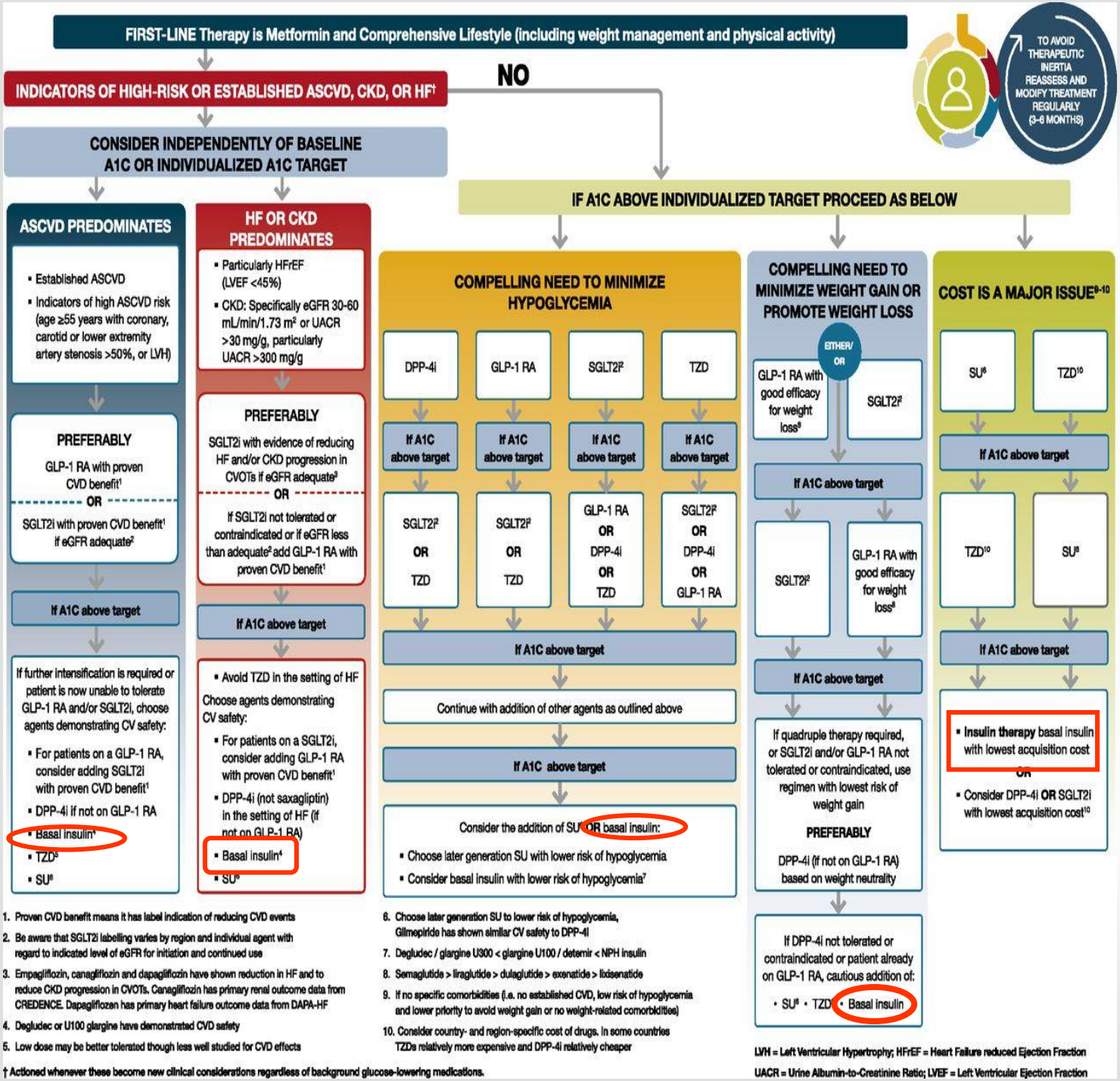
- Diabetes is a progressive disease, but individuals and their treatment requirements also change over time

- Inter-subject dynamism
- Intra-subject dynamism

MANAGEMENT TARGETS SHOULD NOT BE FIXED (GLYCAEMIA & THERAPY)

NO ONE SIZE FITS ALL!

Glucose-lowering Medication in Type 2 Diabetes: Overall Approach



Pharmacologic Approaches to Glycemic Management: *Standards of Medical Care in Diabetes - 2020. Diabetes Care* 2020;43(Suppl. 1):S98-S110

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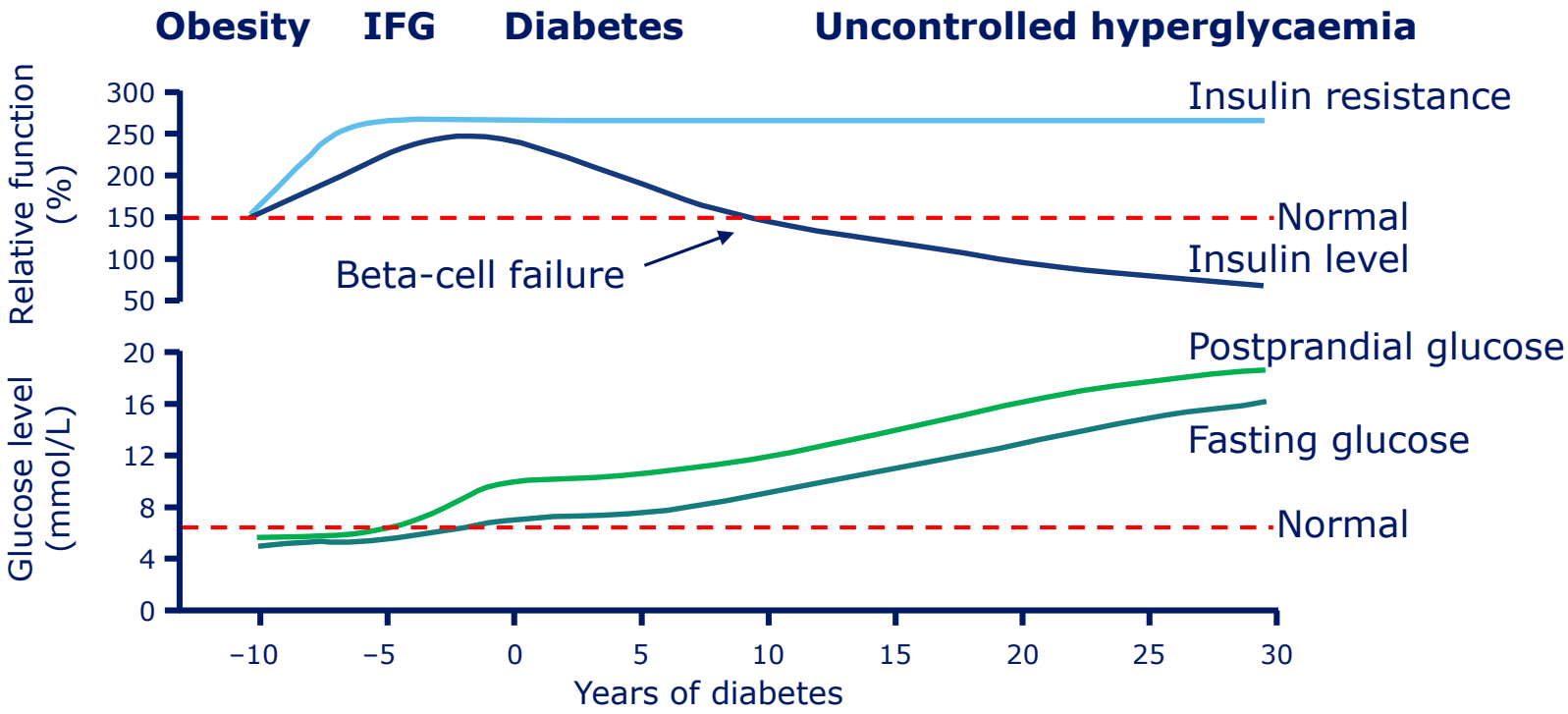
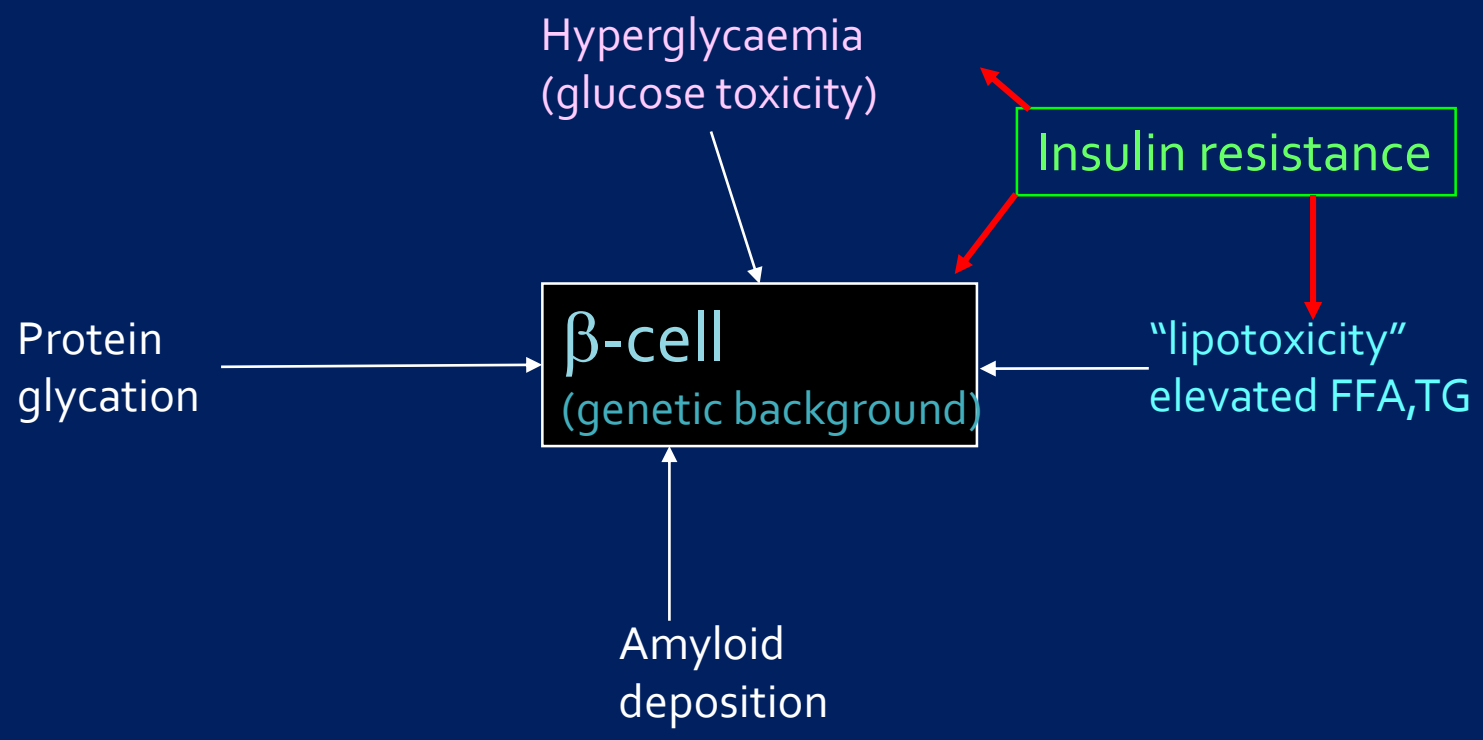
Insulin replacement therapy becomes necessary in most cases



IFG, impaired fasting glucose

Adapted from Bergenstal *et al. Endocrinology*. 4th ed. 2001;821–35

Multiple factors may drive progressive decline of β-cell function



INTRODUCTION OF INSULIN EARLIER IN THE TREATMENT PARADIGM

In vitro studies :

- Chronic hyperglycemia leads to increased production of reactive oxygen species, and subsequent oxidative stress:
  - affect insulin promoter activity (PDX-1 and MafA binding) diminished insulin gene expression in glucotoxic β-cells.
- Glucotoxic effects occur in a continuum of glucose concentrations (no clear threshold effect),
  - are reversible with reinstitution of euglycemic conditions
  - result in the greatest recovery of β-cell function with shorter periods of exposure to hyperglycemia .

Early Insulinization Prevents the Progressive β-cell Dysfunction

Early intensive insulin therapy has favorable outcomes on recovery and maintenance of β-cell function compared with oral hypoglycemic agents

Insulin provides a type of β-cell rest and reduce excessive secretory demands on damaged β-cell

Weng JP et al. Lancet, 2008, 301:1753-1780

Rationale for early initiation of insulin

- Insulin possesses anti-inflammatory and antioxidant properties that may help protect against endothelial dysfunction and damage resulting in vascular disease.

- Insulin therapy and the achievement of good glycemic control earlier in T2DM provide long-term protection to end organs via "**metabolic memory**" regardless of subsequent treatments and degree of glycemic control.

Goal of Insulin Therapy

We are trying to duplicate how the pancreas works in releasing insulin for someone who doesn't have diabetes.

Prandial insulin secretion

***Cephalic phase* of insulin secretion[1]**

- Evoked by the sight, smell and taste of food (before gut absorption)

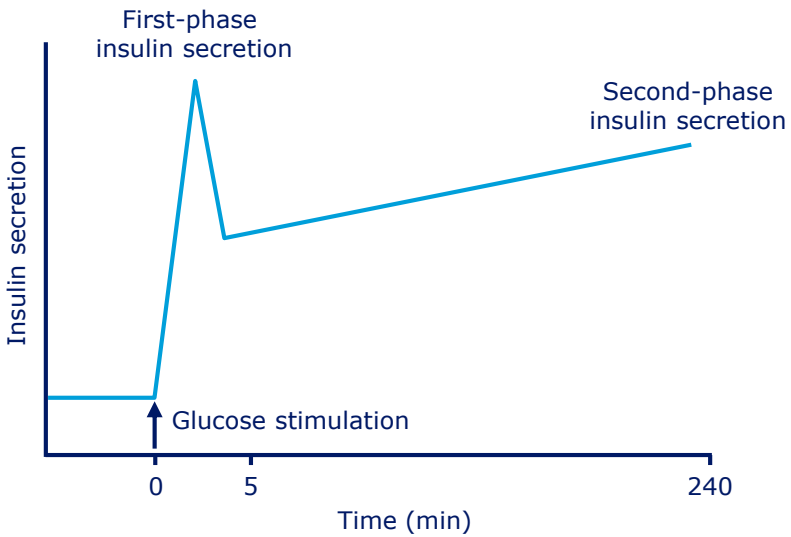
Postprandial *biphasic* insulin secretion[2]:

- *First phase/early phase*, transitory:
  - Critical role in PPG homeostasis (targeting the liver)
  - Can prevent chronic postprandial hyperglycaemia (glucotoxicity) and chronic hyperinsulinaemia (beta-cell exhaustion)
- *Second phase*, more gradually:
  - Related to the degree and duration of the stimulus

β-cell insulin content[3]:

- 2–3% released during first phase
- 20% released during second phase

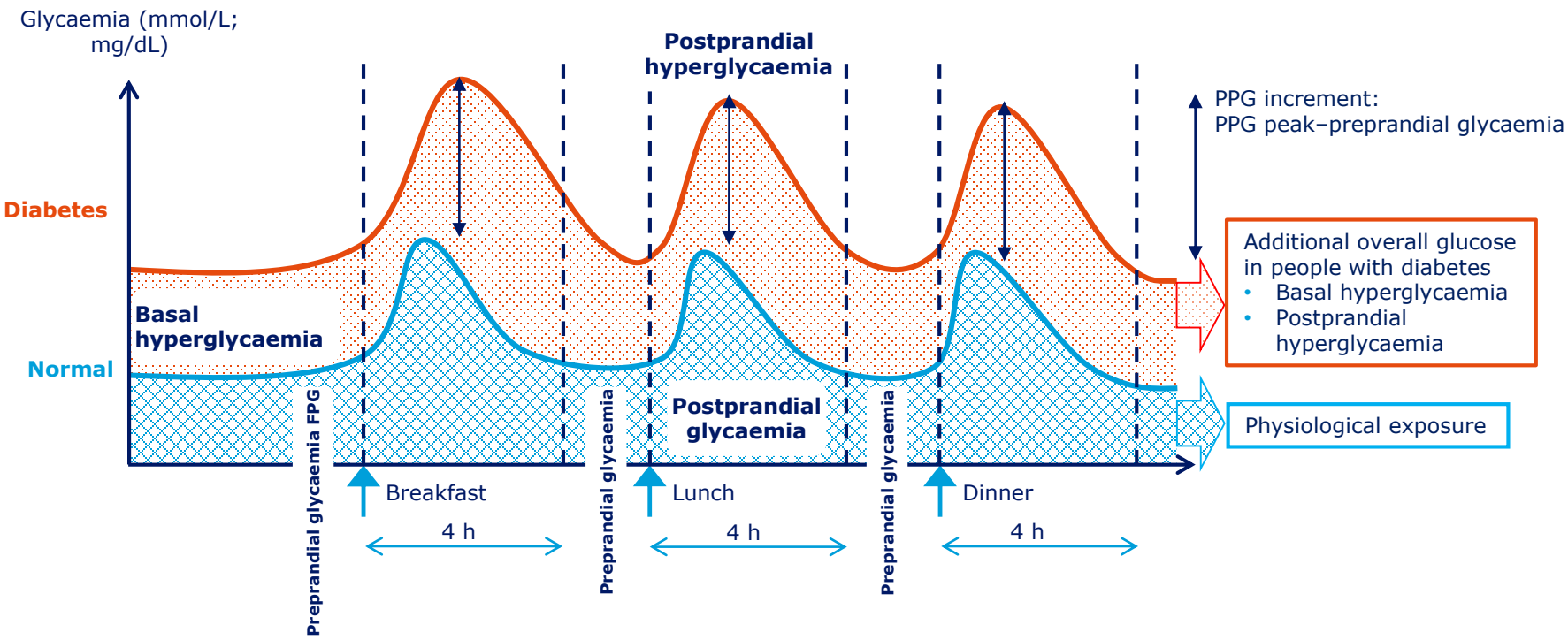
First- and second-phase insulin secretion in the β-cell[4]



PPG, postprandial plasma glucose

Bruce *et al*. *Metabolism* 1987;36:721–5; 1. Caumo & Luzi. *Am J Physiol Endocrinol Metab* 2004;287:E371–85; 2. DelPrato. *Diabetologia* 2003;46(Suppl. 1):2–8; 3. Cheng *et al*. *Curr Molec Med* 2013;13:126–39

Overall glucose exposure is the sum of physiological, basal and postprandial exposures

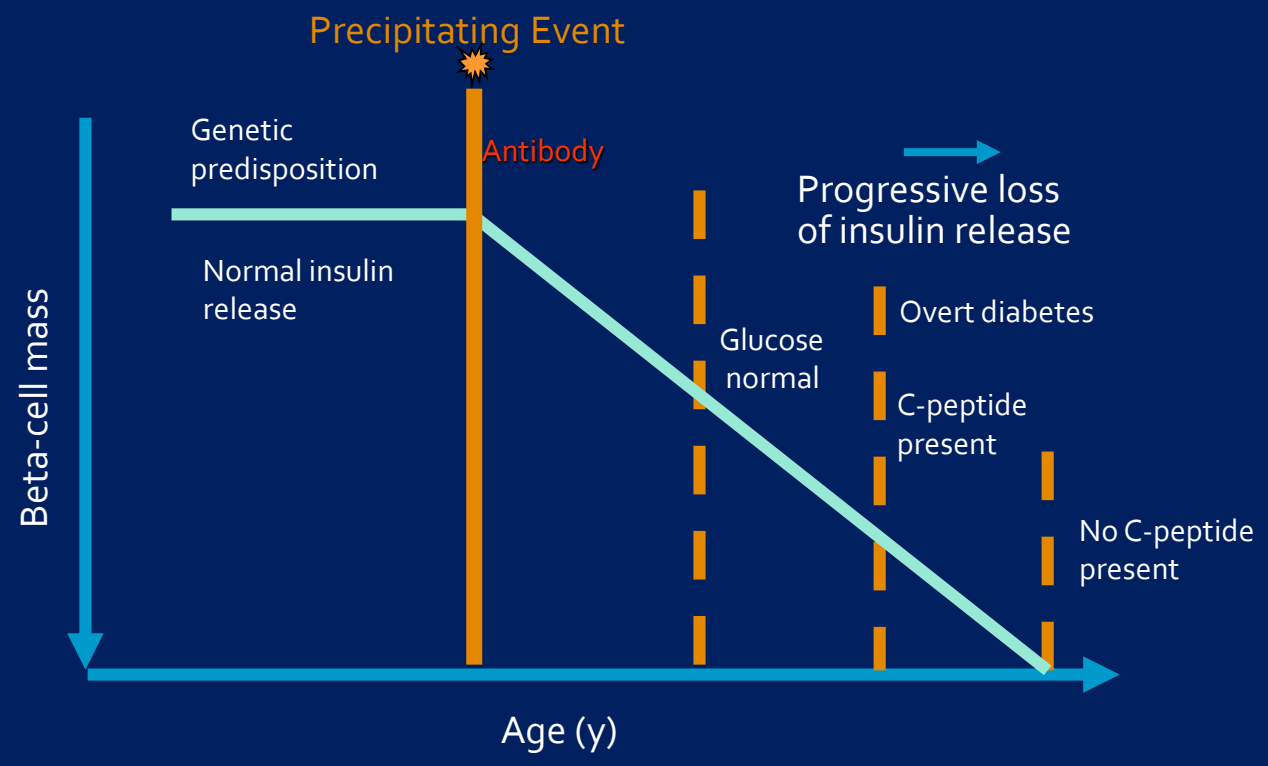


Schematic representation. Adapted from Monnier & Colette. *Diabetes Metab* 2015;41:179–82

Which Patients Need Insulin?

- Type 1 diabetes
- Type 2 diabetes
- Atypical presentations
- Pancreatic insufficiency

Progression of Type 1 Diabetes



Adapted from: Atkinson. *Lancet.* 2002;358:221-229.

Indications for insulin

- Severe hyperglycemia on presentation
- Patients presenting with symptomatic (eg, weight loss) or severe hyperglycemia with ketonuria
- For patients presenting with severe hyperglycemia (FBG >250 mg/dL, random glucose consistently >300 mg/dL, A1C >10 percent but <u>without ketonuria or spontaneous weight loss, in whom type 1 diabetes is not likely</u>, insulin is an option (along with metformin and/or a glucagon-like peptide-1 [GLP-1] receptor agonist), if no contraindications).

Indications for insulin

- **Difficulty distinguishing type of diabetes**
  - Patients who are initially thought to have type 2 diabetes may actually have type 1 diabetes.
  - **Although the peak incidence of type 1 diabetes occurs around the time of puberty, approximately 42 percent of cases present after 30 years of age.**

Indications for insulin

- **Persistent hyperglycemia on oral agents** — Oral agents become less effective as beta cell function declines.

- Insulin is always effective and is preferred in insulin-deficient, catabolic diabetes (eg, polyuria, polydipsia, weight loss).

❖ Patients should be made aware **that initiating insulin does not represent a personal "failure"** and that many patients with type 2 diabetes will eventually require exogenous insulin, due to decline in endogenous insulin production.

Indications for insulin

- It is common practice to initiate insulin therapy for patients who present with
  - blood glucose levels >300 mg/dL (16.7 mmol/L) or
  - A1C.10% (86 mmol/mol) or
  - if the patient has symptoms of hyperglycemia (i.e., polyuria or polydipsia) or evidence of catabolism (weight loss).

✓ As glucose toxicity resolves, simplifying the regimen and/or changing to oral agents is often possible.

Diabetes Care Volume 43, Supplement 1, January 2020

Basal vs. Bolus

- **Basal Insulin**

  In someone without diabetes, the pancreas delivers a small amount of insulin continuously to cover the body's non-food related insulin needs.

- **Bolus Insulin**

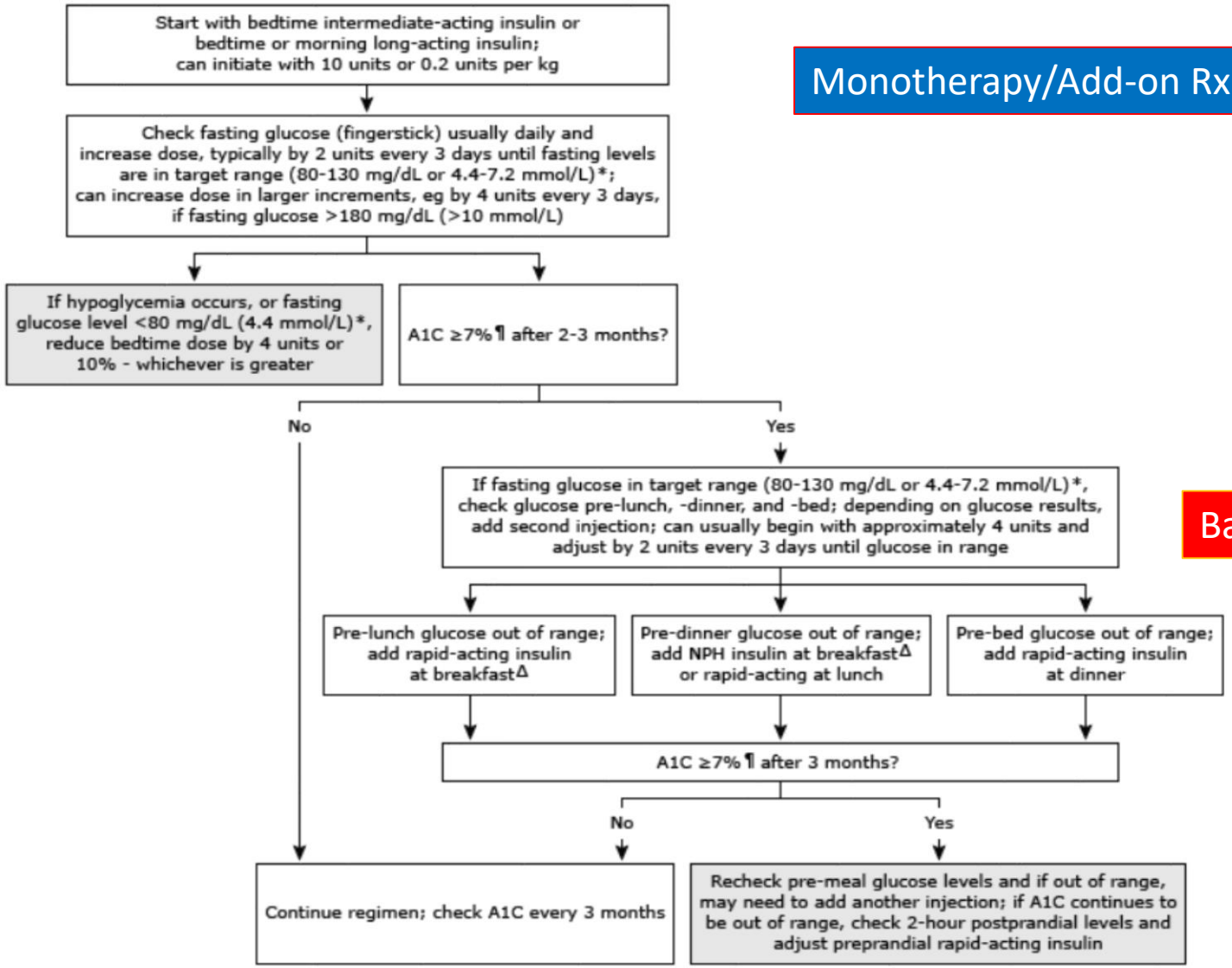
  The amount of insulin required to cover the food you eat.

  Fast-acting or Short-acting (clear) insulin works as a Bolus Insulin.

Options in Insulin Therapy for Type 2 Diabetes

- Add-on therapy (Basal insulin + OAD)
- Basal-plus
- Basal-Bolus

Initiation and adjustment of insulin regimens in type 2 diabetes mellitus



Insulin regimens should be designed taking lifestyle and meal schedule into account. The algorithm can only provide basic guidelines for initiation and adjustment of insulin.

A1C: glycated hemoglobin.

* Glucose levels updated with data from: American Diabetes Association. Glycemic Targets. Diabetes Care 2016; 39 Suppl 1:S39.

Insulin remains the most potent antihyperglycemic agent available for uncontrolled T2DM patients

Intervention	Expected ↓ in HbA_{1c}
Insulin	No upper limit
Metformin	1.5%
Sulfonylureas	1.5%
Glinides	1 to 1.5%[a]
TZDs	0.5 to 1.4%
α-Glucosidase inhibitors	0.5 to 0.8%
GLP-1 agonist	0.5 to 1.0%
DPP-IV inhibitors	~0.8%
SGL2i	Up to 1%

"Insulin will make me fat," and other patient concerns you'll need to overcome

Patient concern	How you can respond
Fear: "I'm afraid of needles."	Insulin pens and smaller, thinner needles make injections almost painless.
Failure: "Going on insulin proves I can't take control of my disease."	The natural course of diabetes is to worsen over time, but controlling your blood glucose levels with insulin can slow that process down.
Stigma: "If people see me taking an insulin shot, they'll think I'm a sick person."	New injection devices like insulin pens are not very noticeable, and the needles are smaller and thinner than they used to be.
Weight gain: "Insulin will make me fat."	I'll help you find a nutritionist who can teach you how to eat healthier foods and develop an active lifestyle that helps keep you trim. And insulin is no more likely to make you fat than some of the oral agents you've been using.
Hypoglycemia: "I've heard that diabetics who use insulin can pass out suddenly, or even go into a coma. I think it's called hypoglycemia, and it scares me."	That's less likely to happen with the newer forms of insulin we use now. And if you do have a hypoglycemic episode, it will probably be something mild you can treat yourself. I can teach you how to recognize what's happening and what to do about it.
Complexity: "It all sounds too difficult for me to manage on my own."	We have new, step-by-step instructions you can follow when you start insulin therapy and when you need to make changes.
Complications: "I know people on insulin who have serious complications like heart attacks and kidney disease. Will that happen to me?"	Diabetes-related complications are the result of inadequate control of blood sugar levels. Insulin provides more intensive glycemic control than you've been achieving, and that helps avoid the complications you're concerned about. That's why I recommend you start using insulin.

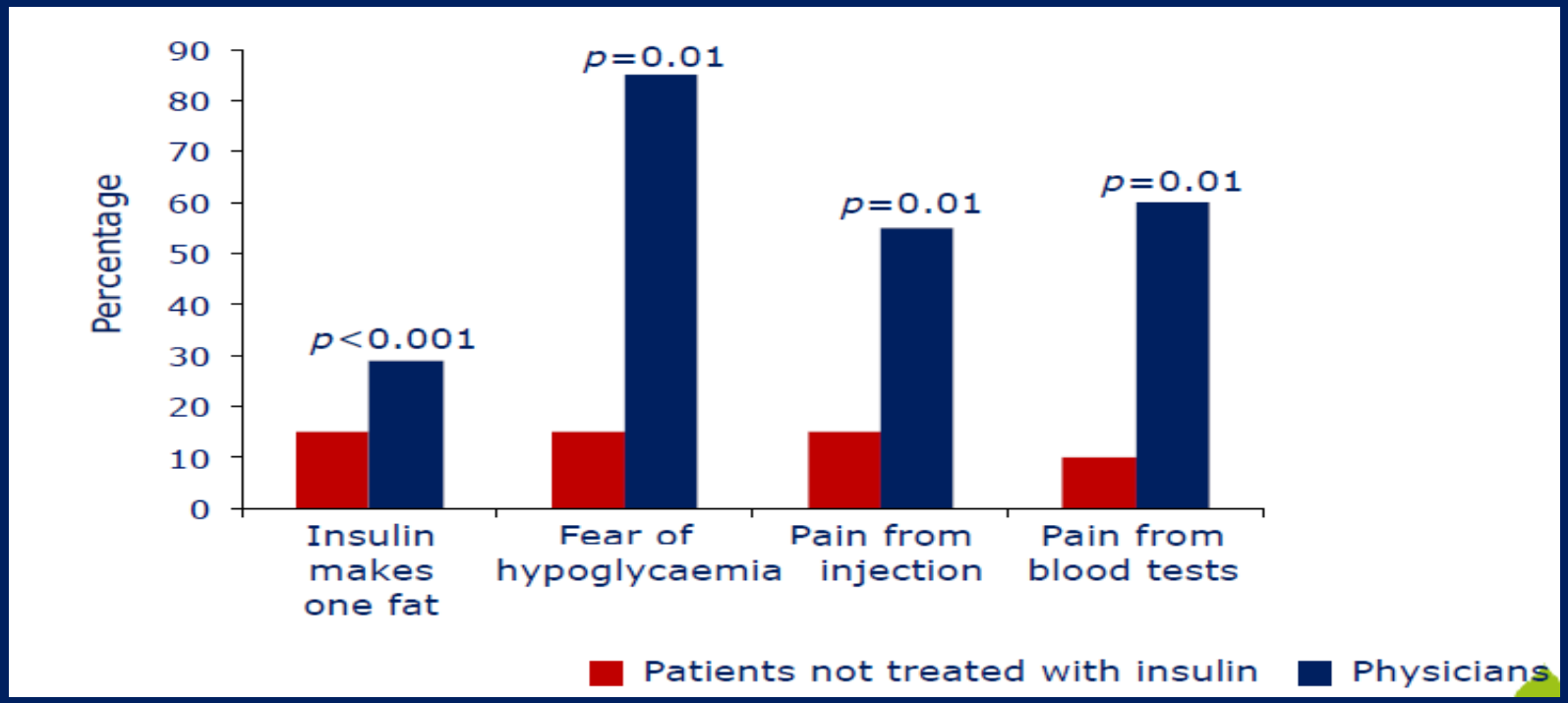
Source: Brunton S, et al. The role of basal insulin in type 2 diabetes management. *J Fam Pract*. 2005.[11]

Physician barriers

- Physicians may be reluctant to initiate insulin due to:[1-3]
  - beliefs about patient risk
  - excess weight gain
  - risks in patients with comorbidities
  - hypoglycaemia
  - impaired quality of life
  - resource issues
  - beliefs about patient competence

1. Peyrot *et al. Diabetes Care* 2005;28:2673–9; 2. Elgrably *et al. Diabet Med* 1991;8:773–7; 3. Wallace & Matthews. *QJM* 2000;93:369–74

Barriers to insulin initiation



Nakar et al. J Diabetes Complications 2007;21:220–6

‘wait until next visit’ approach

A ‘wait until next visit’ approach is often adopted, particularly when faced with soft rationalizations by patients to avoid treatment intensification.

Use of Empowering Language

Five key consensus recommendations for language use:

1. Use language that is neutral, nonjudgmental, and based on facts, actions, or physiology/biology;
2. Use language that is free from stigma;
3. Use language that is strength based, respectful, and inclusive and that imparts hope;
4. Use language that fosters collaboration between patients and providers;
5. Use language that is person centered (e.g., “person with diabetes” is preferred over “diabetic”).

American Diabetes Association.
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Conclusion

- In North America alone, where there are approximately 36.7 million people with diabetes, this equates to nearly 30 million people who are inadequately controlled.

- This is responsible for an excess of at least **200,000 avoidable diabetes-related complications per year**, which in turn is responsible for billions of dollars in excess health care charges and tens of thousands of premature deaths.

Conclusion

- The main advantage of insulin over other glucose-lowering medications is that insulin lower glucose in a dose dependent manner over a wide range, to almost any glycemic target as limited by hypoglycemia.
- Greater improvement in β-cell function (Reduces Glucotoxicity & Lipotoxicity)
- Reverses insulin resistance

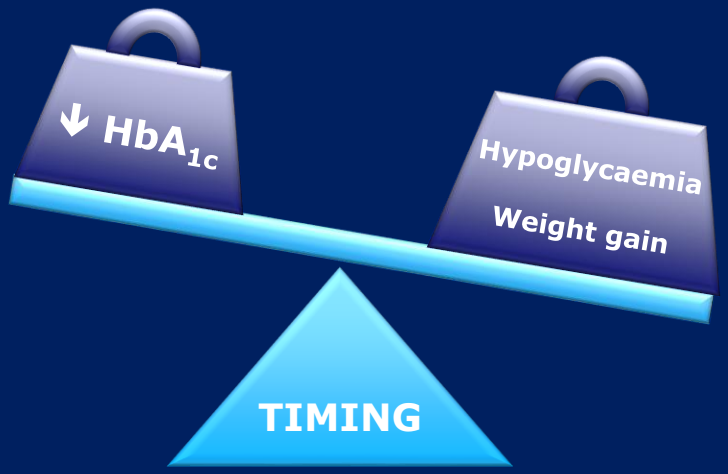
Conclusion

- **The effectiveness of insulin is highly dependent on**
  - appropriate use;
  - patient selection and training;
  - adjustment of dose for changes in diet, activity, or weight;
  - titration to acceptable, safe glucose targets.

- Formulations of rapid, intermediate- and long-acting insulin have different timings of onset, durations of action, and risks of hypoglycemia.

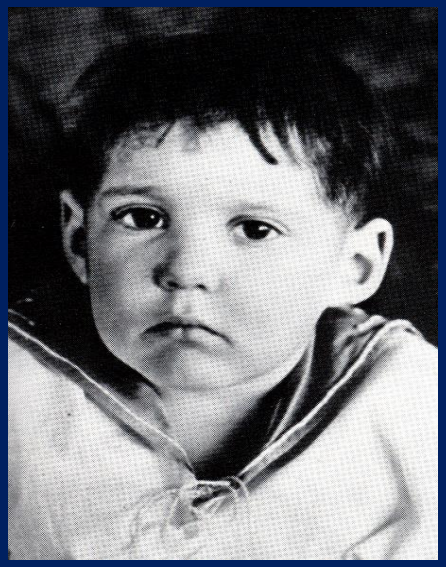
Balancing glycaemic control and side effects

- Clinicians must balance glycaemic control with side effects associated with current type 2 diabetes treatments, including insulin



The Miracle of Insulin

Patient J.L., December 15, 1922



February 15, 1923

Thank You
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