Treating Earlier and Effectively with Combination Therapies

International Diabetes Federation

FEND
Federation of European Nurses in Diabetes

CONTROL TO GOAL

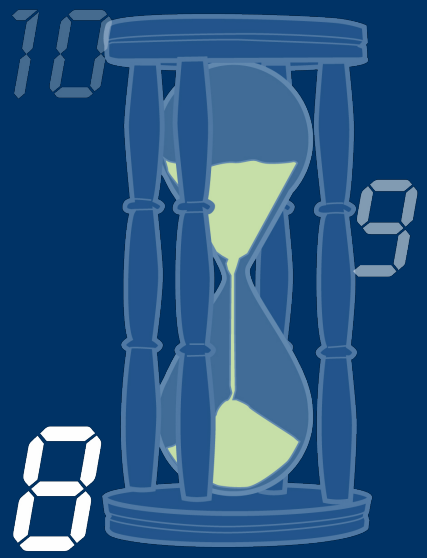
Aim

Provide practical guidance on improving diabetes care through highlighting the need for:

- a sense of urgency in treating to target
- earlier introduction of combination therapy
- consideration of patient profile
- use of combinations of drugs with complementary mechanisms of action

Need for an early and intensive approach to type 2 diabetes management

- At diagnosis of type 2 diabetes:
  - **50%** of patients already have complications[1]
  - up to **50%** of β-cell function has already been lost[2]
- Current management:
  - **two-thirds** of patients do not achieve target HbA_{1c}[3,4]
  - **majority** require polypharmacy to meet glycemic goals over time[5]



[1]UKPDS Group. *Diabetologia* 1991; 34:877–890. [2]Holman RR. *Diabetes Res Clin Prac* 1998; 40 (Suppl.):S21–S25. [3]Saydah SH, *et al. JAMA* 2004; 291:335–342.
[4]Liebl A, *et al*. *Diabetologia* 2002; 45:S23–S28. [5]Turner RC, *et al*. *JAMA* 1999; 281:2005–2012.

Barriers to achieving good glycemic control

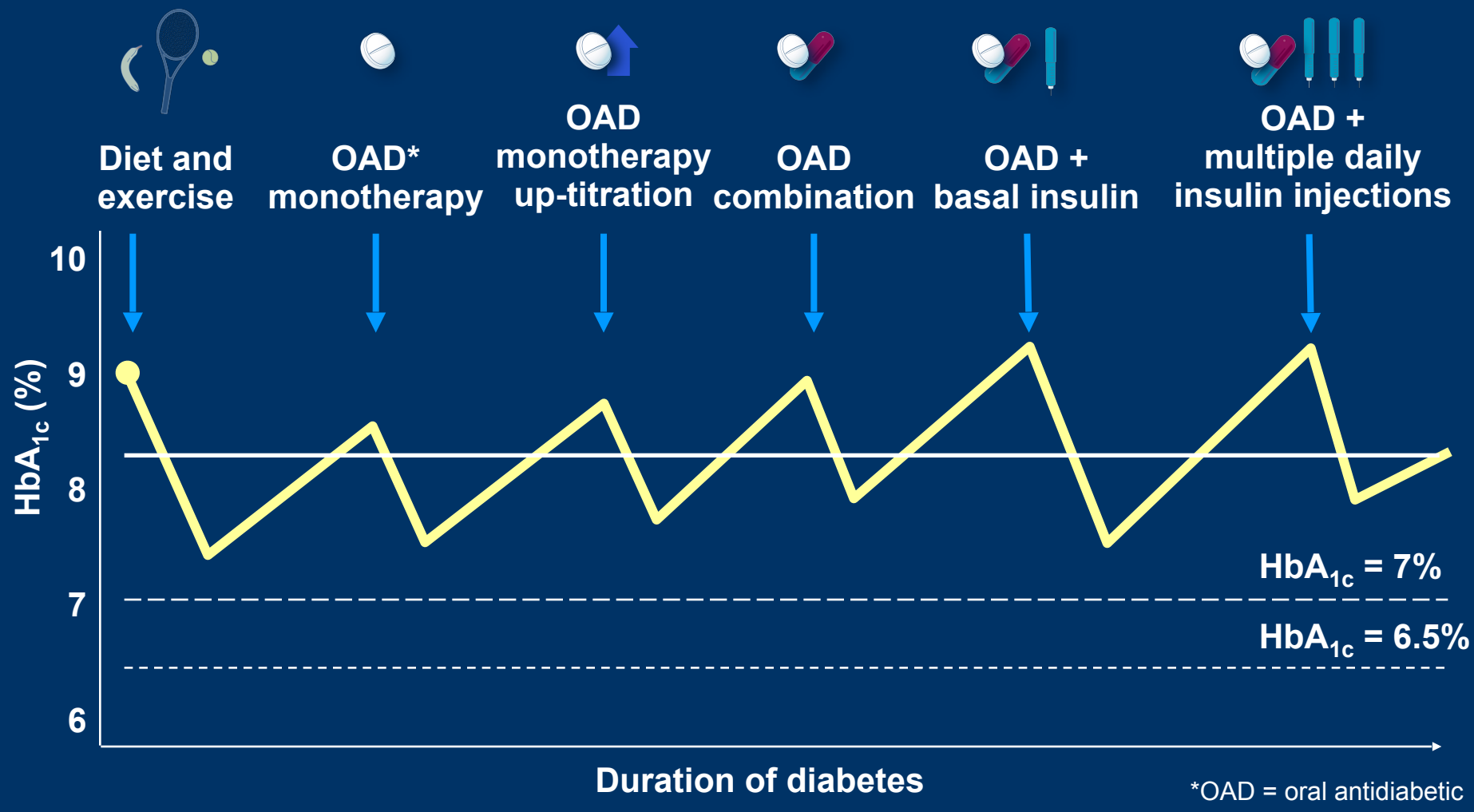
Limitations of reactive, stepwise treatment

Therapy not matched to the individual

Conservative prescribing of antidiabetic agents

Limitations of reactive, stepwise treatment

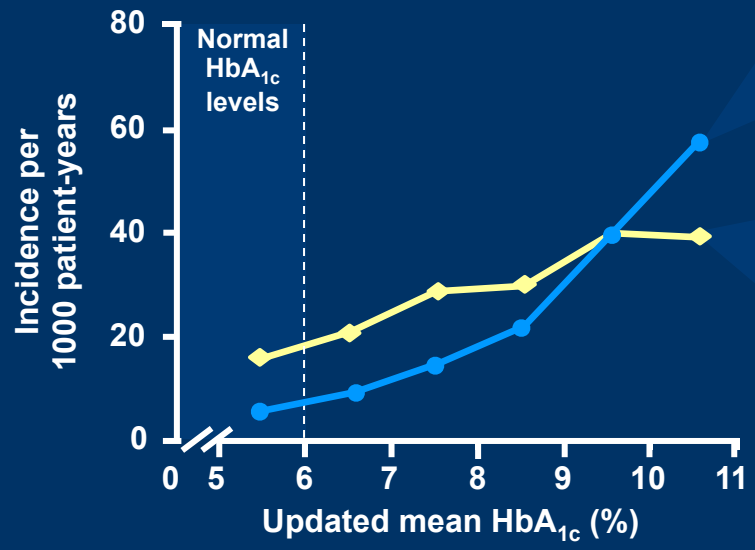
Conservative management of glycemia: traditional stepwise approach

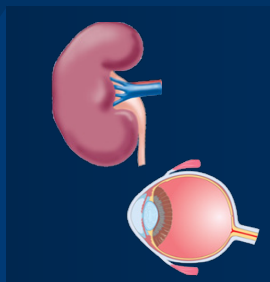


Campbell IW. *Br J Cardiol* 2000; 7:625–631.

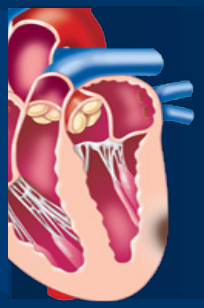
Drawbacks of the stepwise approach

- Even short periods of hyperglycemia increase risk of complications[1–3]
- A proactive approach is required to get patients to achieve their glycemic goals sooner





Microvascular complications



Myocardial infarction

[1]EDIC Group. *JAMA* 2003; 290:2159–2167. [2]EDIC Group. *JAMA* 2002; 287:2563–2569.
[3]Nathan DM, *et al*. *N Engl J Med* 2003; 348:2294–2303.

Diet and exercise are beneficial to good glycemic control

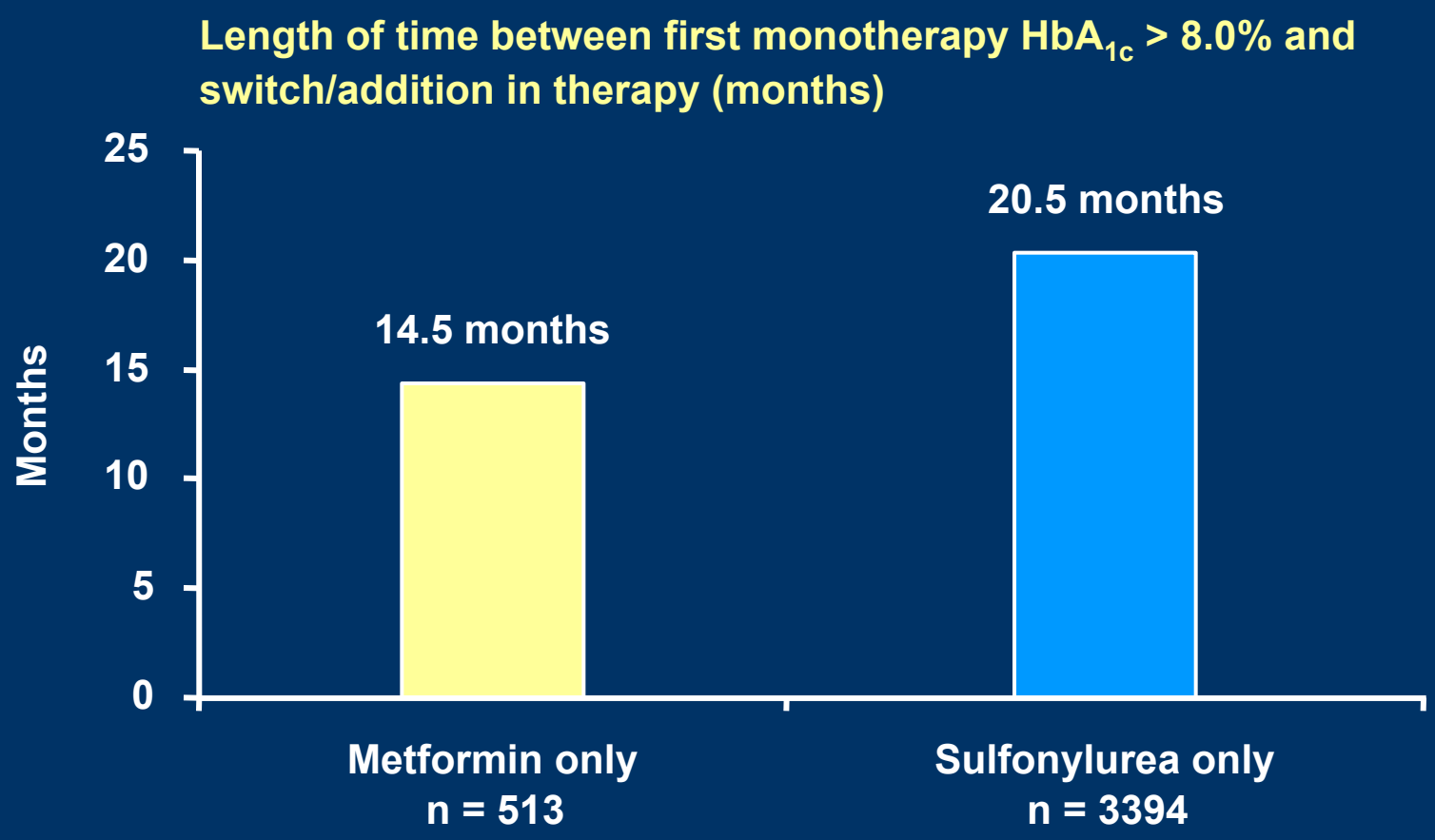
- Lifestyle changes can have beneficial outcomes[1,2]
- Patients may require motivation to encourage them to follow a healthy diet and take exercise

[1]Levy J, *et al. Diabet Med* 1998; 15:290–296.
[2]Macauley KA, *et al*. *Diabetes Care* 2002; 25:442–452.

Benefits of diet and exercise may be difficult to maintain in the long term

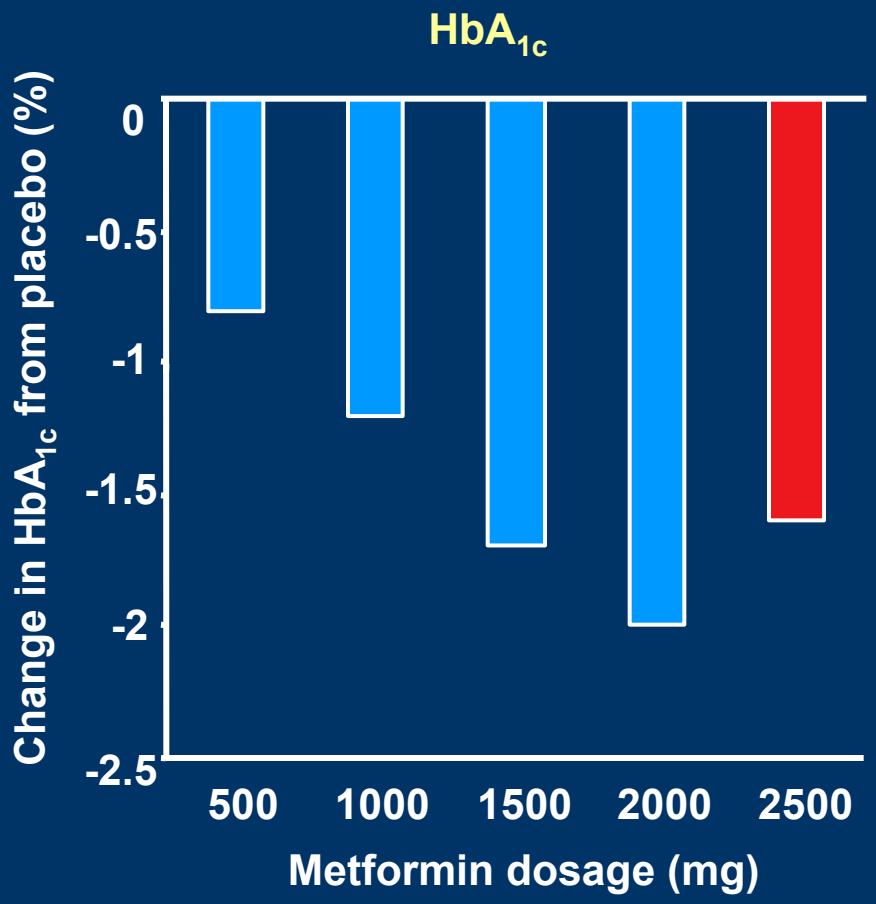
- Stepwise treatment may lead to delays
- Pharmacological therapy should be introduced in tandem with lifestyle changes

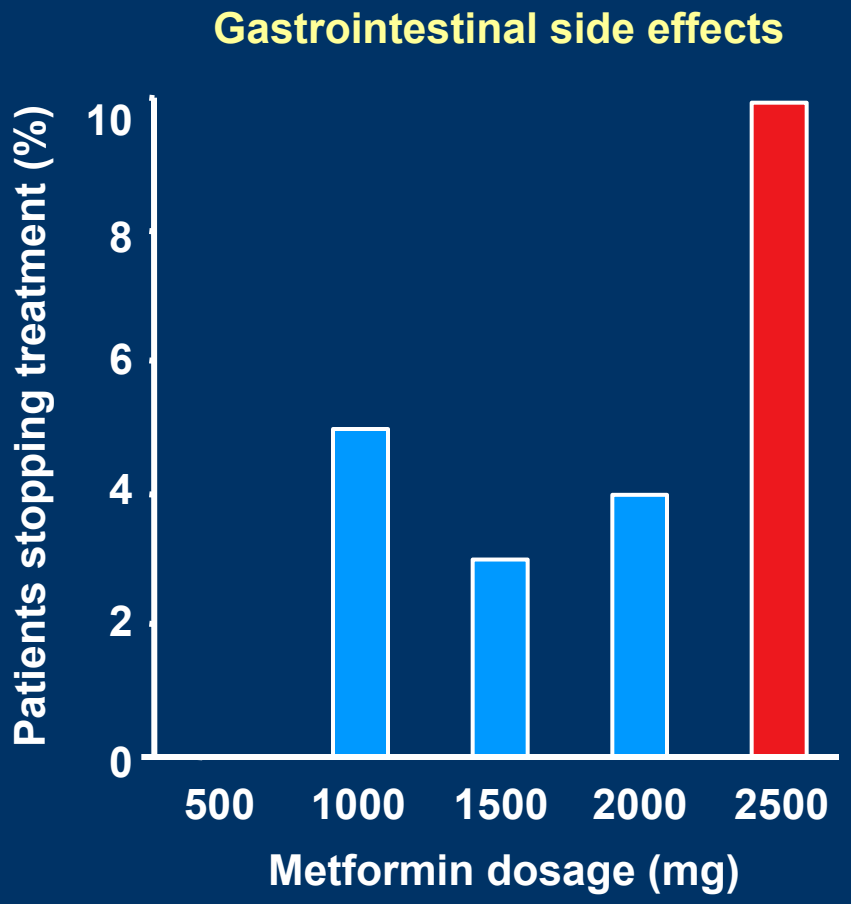
Delays often occur between stepping up from monotherapy to combination therapy



Brown, JB *et al. Diabetes Care* 2004; 27:1535–1540.

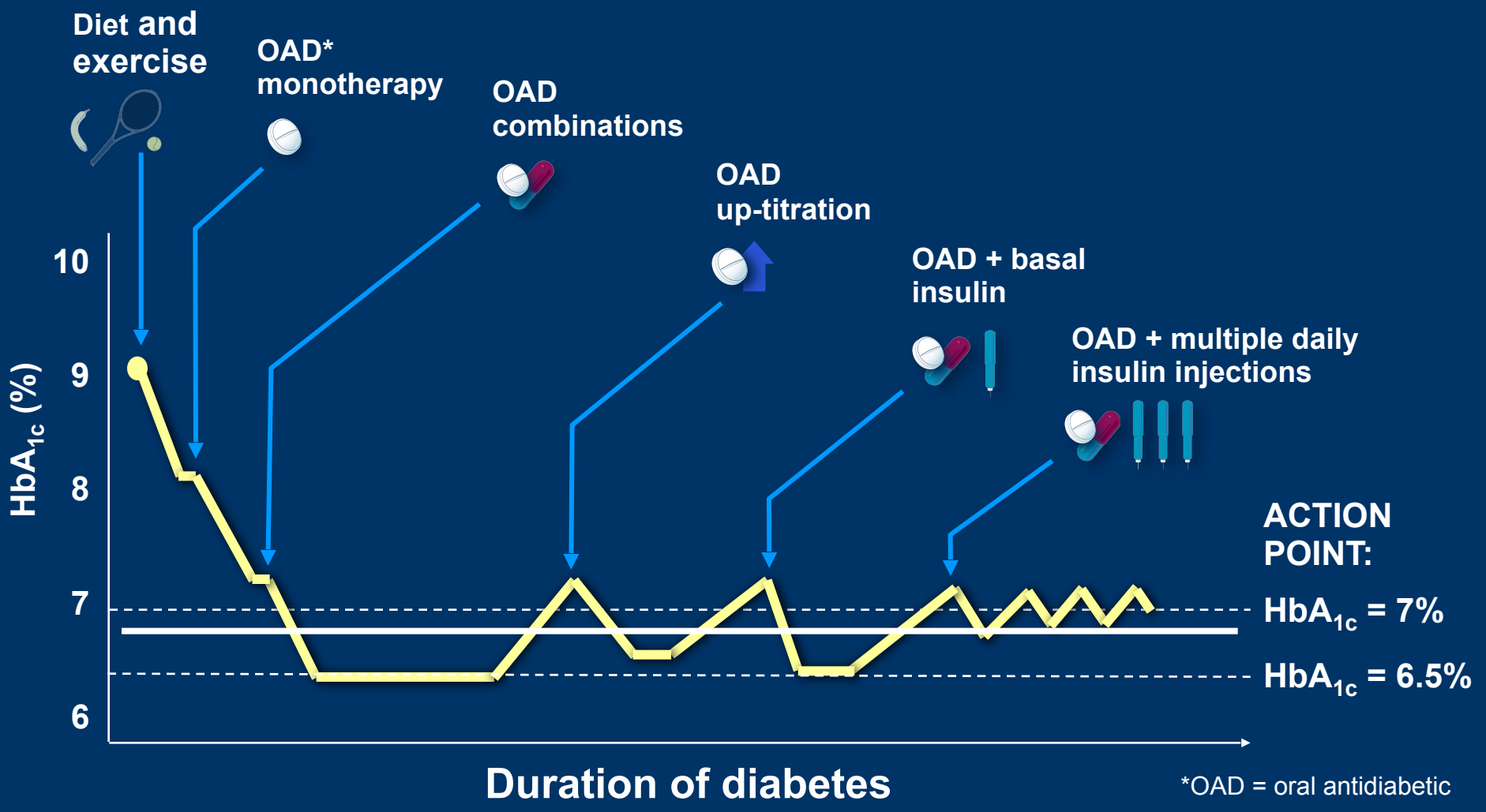
Up-titrating monotherapy to the maximum recommended dose may not provide benefit





Garber AJ, *et al*. *Am J Med* 1997; 103:491–497.

Proactive management of glycemia: early combination approach

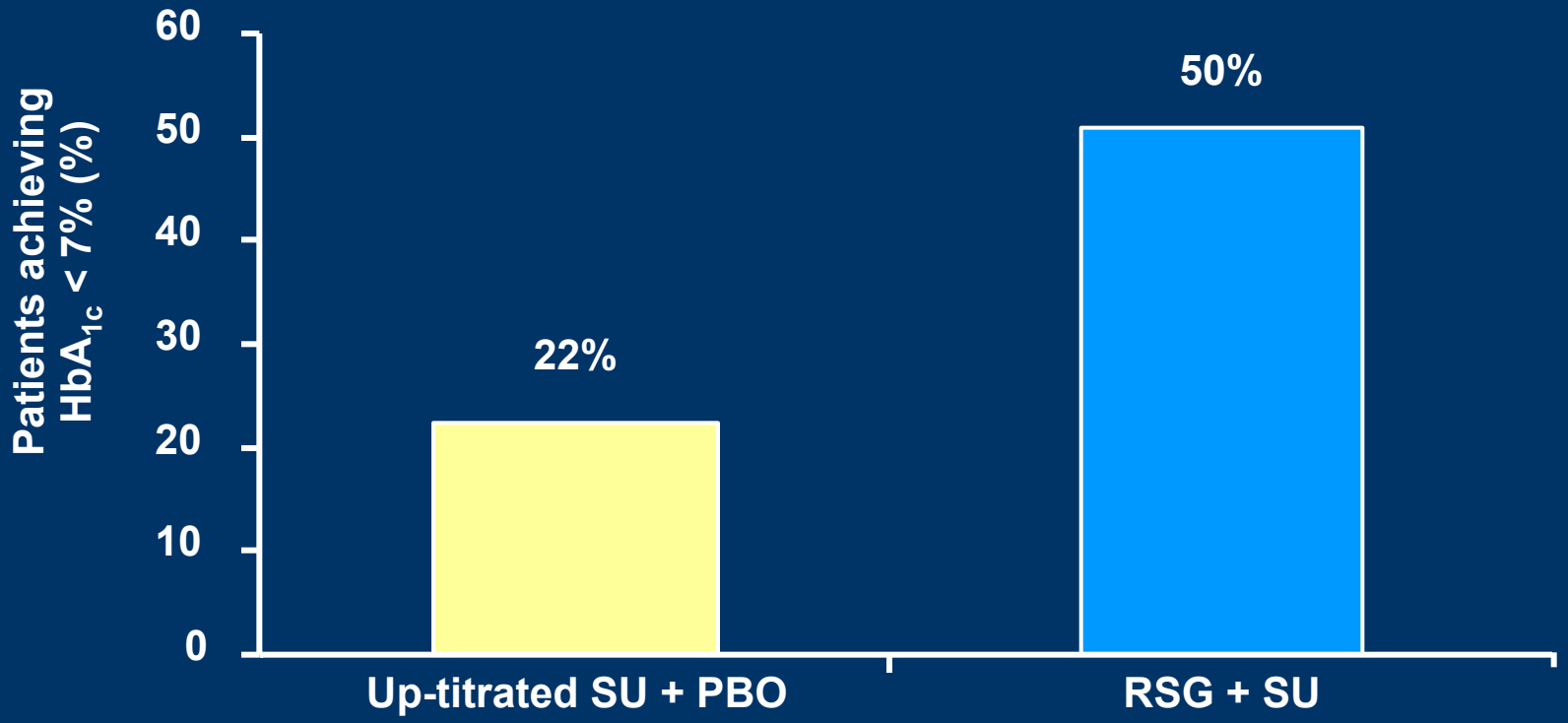


*OAD = oral antidiabetic

Potential advantages of early combination therapy

- Earlier achievement of therapeutic goals
- Potential reduction in risk of side effects if you combine drugs at lower doses versus up-titration of single dose
- Opportunity to combine oral antidiabetic drugs with complementary modes of action
- Potential to delay disease progression

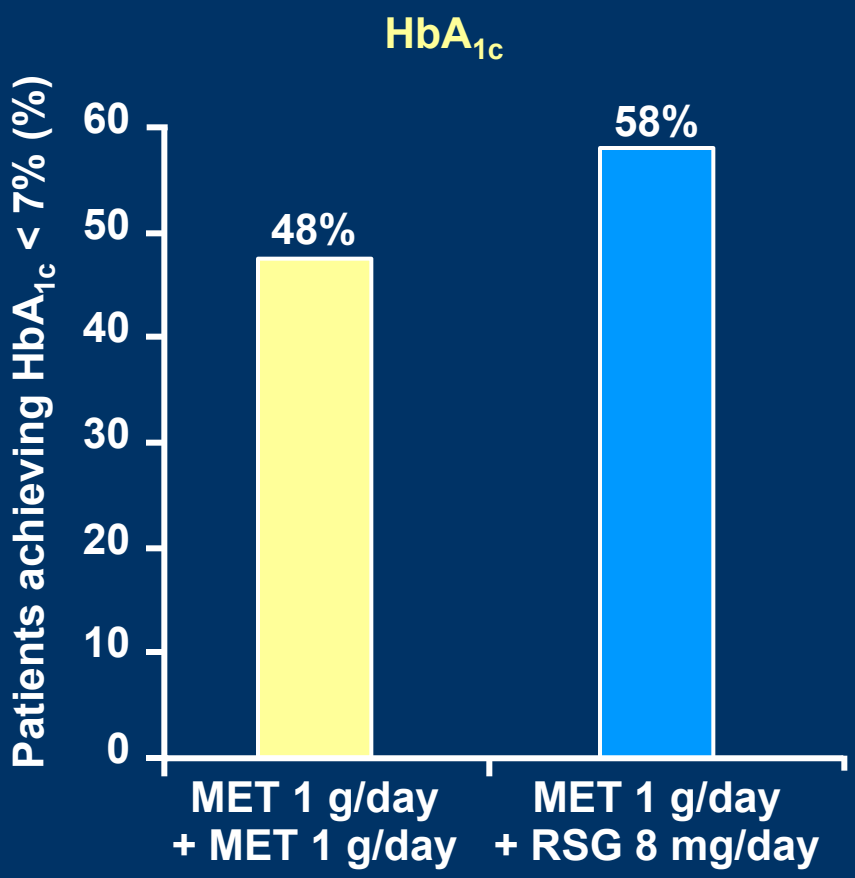
Benefits of adding TZD to sub-maximal sulfonylurea compared with up-titration

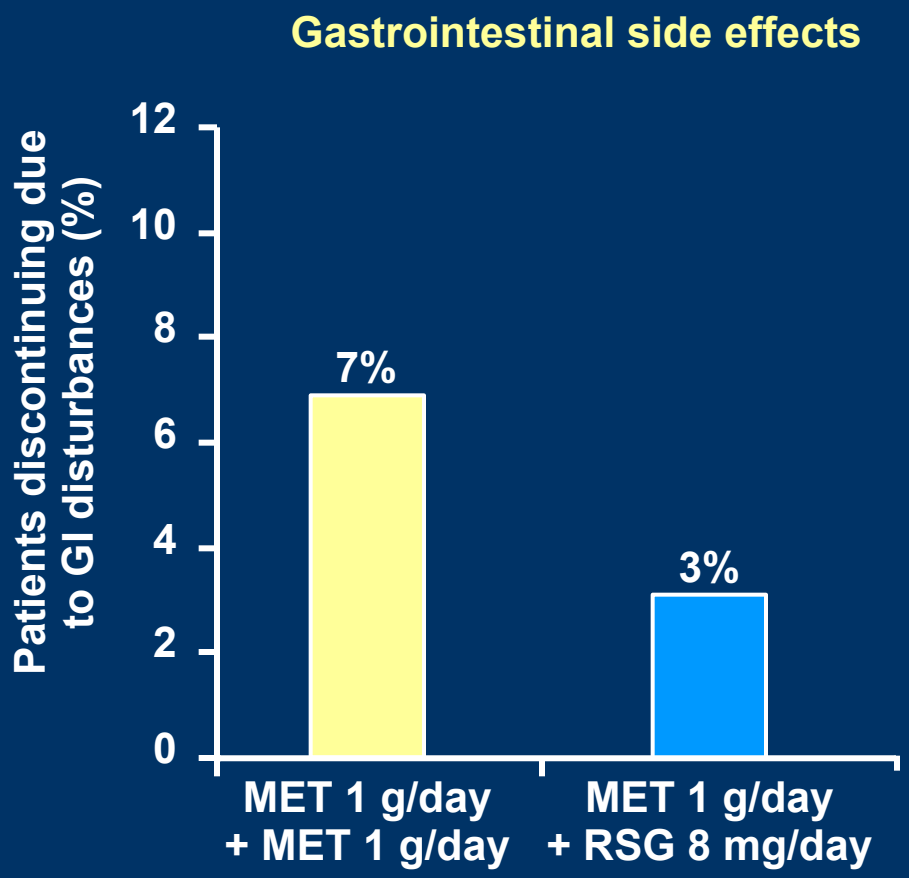


Abbreviations: PBO, placebo; RSG, rosiglitazone; SU, sulfonylurea; TZD, thiazolidinediones.

Rosenstock J, *et al*. *Diabetes Obes Metab* 2005*;* [In press].

Benefits of adding TZD to sub-maximal metformin compared with up-titration

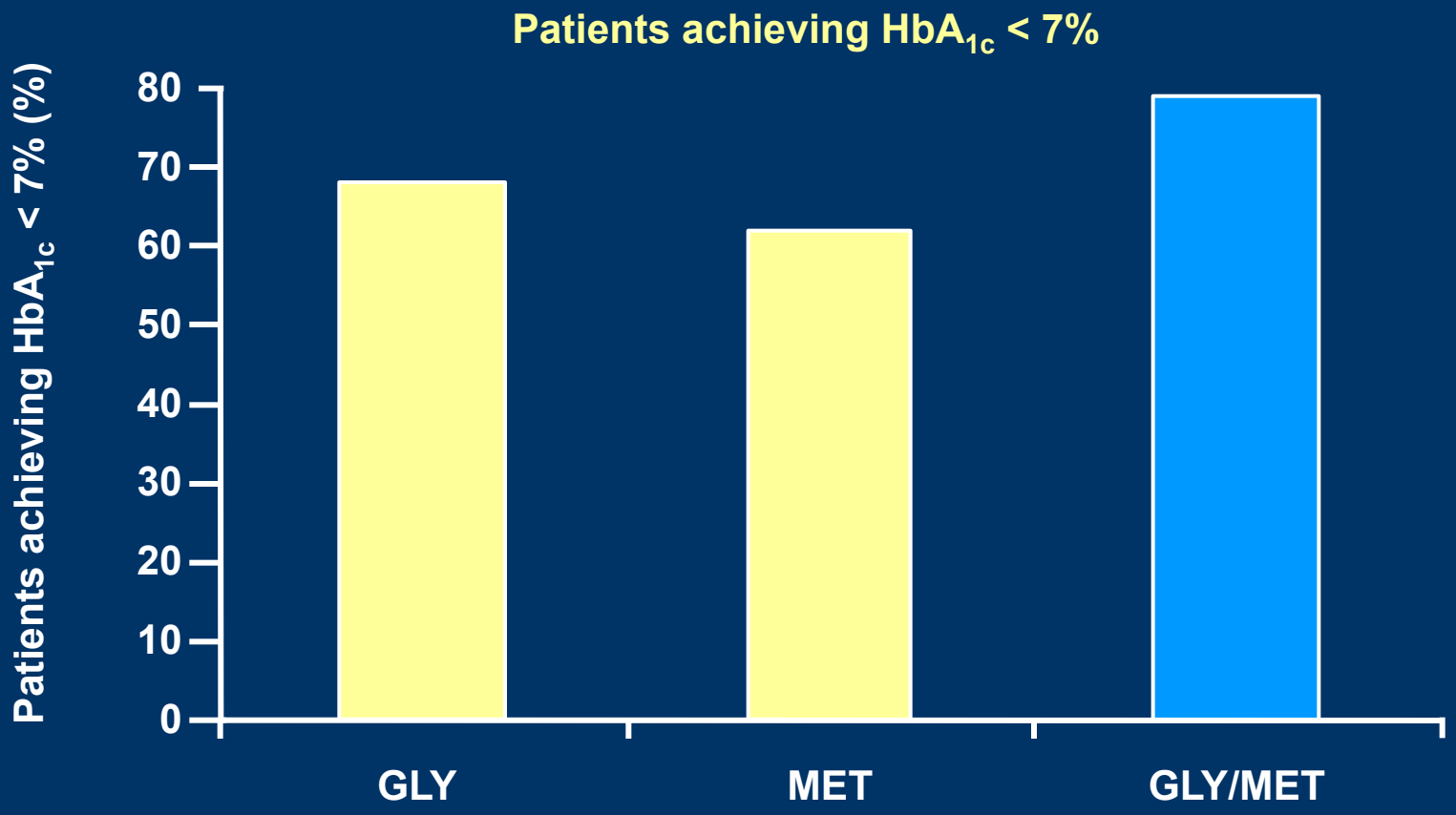




Abbreviations: MET, metformin; RSG, rosiglitazone; TZD, thiazolidinediones.

Rosenstock J, *et al. Diabetes* 2004; 53 (Suppl. 2):A144.

Benefits of glyburide/metformin versus monotherapy as initial pharmacotherapy



Abbreviations: GLY, glyburide; MET, metformin.

Garber AJ, *et al*. *J Clin Endocrinol Metab* 2003; 88:3598–3604.

How quickly should patients be reaching HbA_{1c} targets?

The Global Partnership recommends:

Treat patients intensively so as to achieve target HbA_{1c} < 6.5%* within 6 months of diagnosis

*Or fasting/preprandial plasma glucose < 110 mg/dL (6.0 mmol/L) where assessment of HbA_{1c} is not possible

Del Prato S, *et al. Int J Clin Pract* 2005; 59:1345–1355.

When should combination therapy be introduced?

The Global Partnership recommends:

After 3 months, if patients are not at target HbA_{1c} < 6.5%,* consider combination therapy

*Or fasting/preprandial plasma glucose < 110 mg/dL (6.0 mmol/L) where assessment of HbA_{1c} is not possible

Del Prato S, *et al. Int J Clin Pract* 2005; 59:1345–1355.

Therapy not matched to the individual

Individuals with high baseline HbA_{1c} require more intensive treatment

- Risk of complications increases with HbA_{1c}
- Individuals with high baseline values require particularly urgent and intensive treatment
- Monotherapy is often insufficient in these individuals and combination therapy should be initiated earlier

Stratton IM, *et al. BMJ* 2000; 321:405–412.

How should patients with high baseline HbA_{1c} be managed?

The Global Partnership recommends:

Initiate combination therapy or insulin immediately for all patients with $HbA_{1c} \geq 9\%$ at diagnosis

Del Prato S, *et al. Int J Clin Pract* 2005; 59:1345–1355.

Inappropriate prescribing of antidiabetic agents

Reasons for conservative prescribing patterns

- Familiarity with traditional agents
- Concerns regarding safety of newer agents
- Perceived lack of efficacy of antidiabetic agents

Treatment options for type 2 diabetes

- **Sulfonylureas**
  - 1st generation e.g. chlorpropamide, tolbutamide
  - 2nd generation e.g. glyburide, gliclazide, glipizide, gliquidone
  - 3rd generation e.g. glimepiride
  - Modified release
- **Glinides/meglitinides**
  - Non-sulfonylureic e.g. repaglinide
  - Amino acid derivatives e.g. nateglinide
- **Biguanides**
  - e.g. metformin
- **Thiazolidinediones**
  - e.g. rosiglitazone, pioglitazone
- **α-glucosidase inhibitors**
  - e.g. acarbose
- **Insulin**
  - regular
  - intermediate/long acting
  - pre-mixed
  - analogs
    - rapid acting
    - long acting
- **Fixed-dose oral antidiabetic drug combinations**
  - e.g. glyburide/metformin, glipizide/metformin, rosiglitazone/metformin

Choosing antidiabetic agents: efficacy

EFFICACY	ANTIDIABETIC AGENTS				
	Insulin secretagogues	Metformin	α-glucosidase inhibitors	TZDs*	Insulin
Effect on FPG/HbA_{1c}[1]	↓	↓	↓	↓	↓
Effect on plasma insulin[1,2]	↑	↓	■	↓	↑
Effect on insulin resistance[3]	■	↓ / ■	■	↓	■
Effect on insulin secretion[4]	↑	■	■	↓	–

↓ = reduced levels ↑ = increased levels ■ = no significant effect

*TZDs = thiazolidinediones

[1]DeFronzo RA. *Ann Intern Med* 1999; 131:281–303. [2]Lebovitz HE. *Endocrinol Metab Clin North Am* 2001; 30:909–933.
[3]Matthaei S, *et al. Endocrine Reviews* 2000; 21:585–618. [4]Raptis SA & Dimitriadis GD. *J Exp Clin Endocrinol*; 2001; 109 (Suppl. 2):S265–S287.

Choosing antidiabetic agents: safety and tolerability

SAFETY AND TOLERABILITY	ANTIDIABETIC AGENTS				
	Insulin secretagogues	Metformin	α-glucosidase inhibitors	TZDs*	Insulin
Risk of hypoglycemia[1,2]	✓	■	■	■	✓
Weight gain[1,2]	✓	■	■	✓	✓
Gastrointestinal side effects[1]	■	✓	✓	■	■
Lactic acidosis[1]	■	✓	■	■	■
Edema[3]	■	■	■	✓	■

✓ = treatment-related adverse event

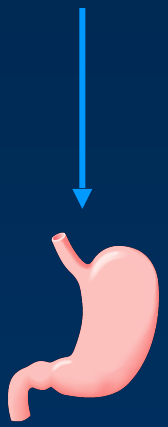
■ = not commonly seen in monotherapy

*TZDs = thiazolidinediones

[1]DeFronzo RA. *Ann Intern Med* 1999; 131:281–303. [2]UKPDS. *Lancet* 1998; 352:837–853.
[3]Nesto RW, *et al. Circulation* 2003; 108:2941–2948.

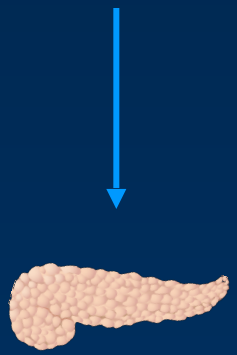
Choosing oral antidiabetic agents: mechanism of action

α-glucosidase inhibitors



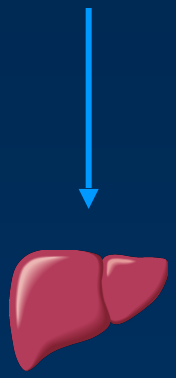
↓ Carbohydrate breakdown/ absorption

Sulfonylureas/ meglitinides



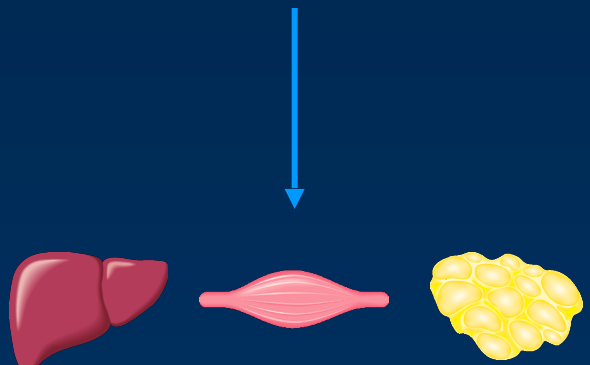
↑ Insulin secretion

Biguanides



↓ Glucose output
↓ Insulin resistance

Thiazolidinediones



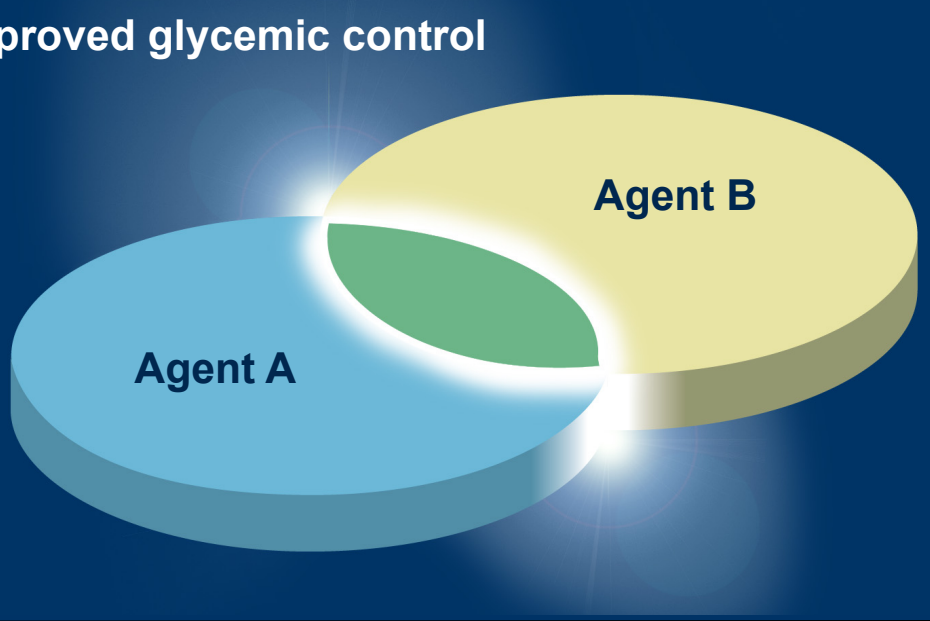
↓ Insulin resistance

[1]Kobayashi M. *Diabetes Obes Metab* 1999; 1 (Suppl. 1):S32–S40.
[2]Nattrass M & Bailey CJ. *Baillieres Best Pract Res Clin Endocrinol Metab* 1999; 13:309–329.

What are the ideal components for combination therapy?

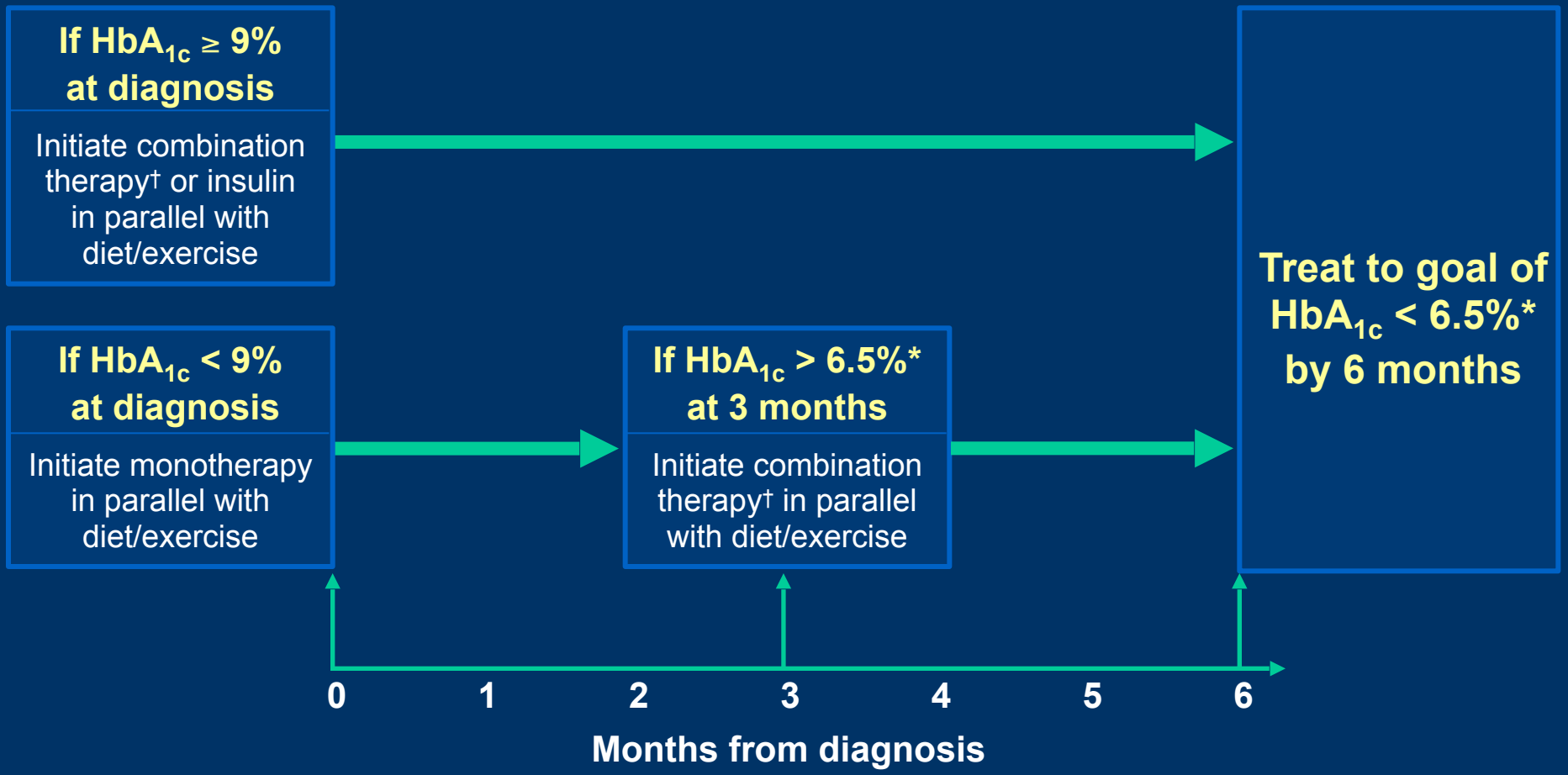
The Global Partnership recommends:

Use combinations of oral antidiabetic agents with complementary mechanisms of action



Del Prato S, *et al. Int J Clin Pract* 2005; 59:1345–1355.

Paradigm for early combination treatment



*Or fasting/preprandial plasma glucose < 110 mg/dL (6.0 mmol/L) where assessment of HbA_{1c} is not possible

†Combination therapy should include agents with complementary mechanisms of action

Del Prato S, *et al. Int J Clin Pract* 2005; 59:1345–1355.