Update in diagnosis and management of diabetes

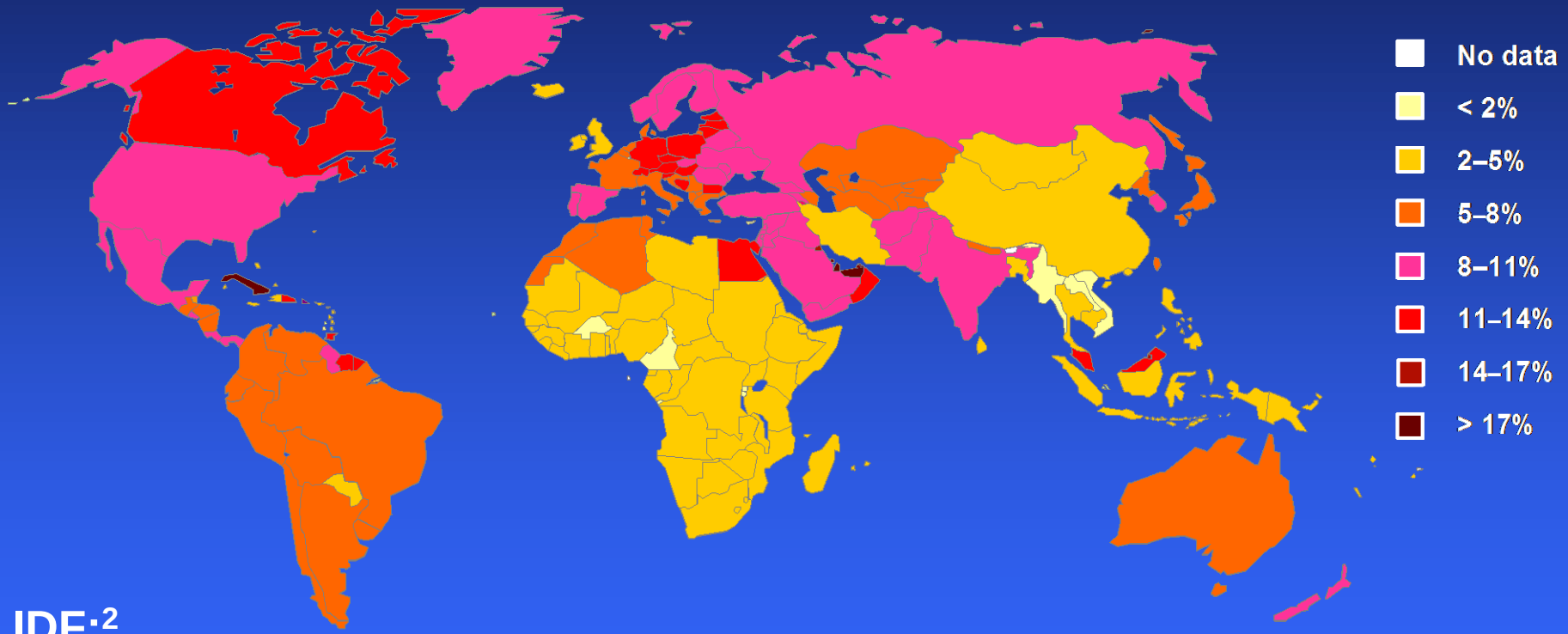
Dr. Doris Chan

Pok Oi Hospital, Medicine & Geriatrics Department

5/4/2016

Diabetes: the growing global burden

Prevalence estimates of diabetes mellitus 2025 [1]



IDF:[2]

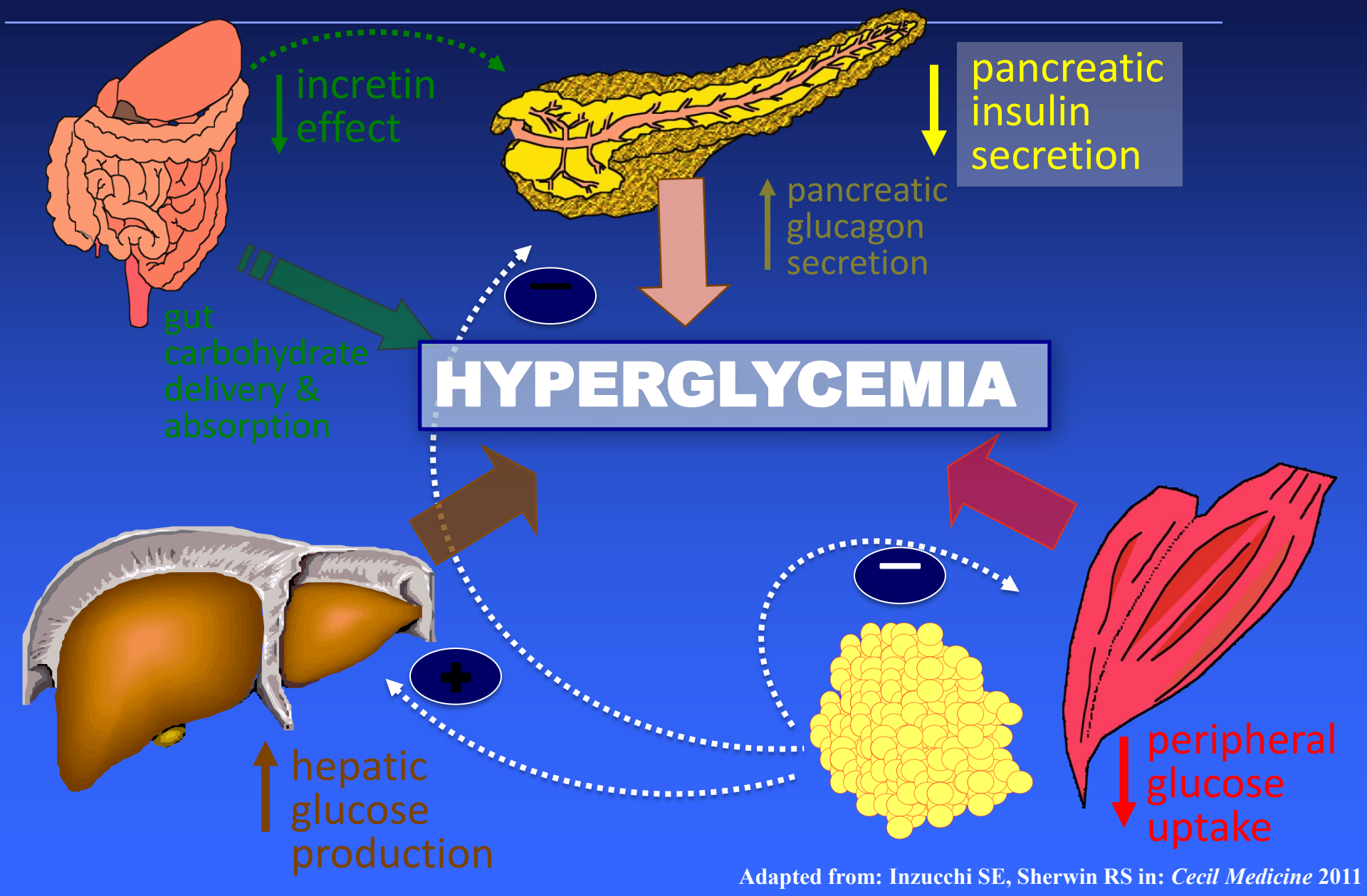
- **Diabetes currently affects 246 million people worldwide**
- **It is expected to affect 380 million by 2025**

[1]Adapted from IDF. E-Atlas. Available at: www.eatlas.idf.org (accessed 05 March 2007).
[2]Diabetes Atlas, third edition © International Diabetes Federation, 2006.

Factors contributing to this growing epidemic

- Reduced physical activity
- Increased in obesity
- Westernization

Main Pathophysiological Defects in T2DM



Adapted from: Inzucchi SE, Sherwin RS in: *Cecil Medicine* 2011

Diagnostic tests for Diabetes

- Plasma glucose criteria
- HbA1c criteria

Table 2.1—Criteria for the diagnosis of diabetes
FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).
*In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

2016 ADA guideline

Type 2 diabetes: Complications



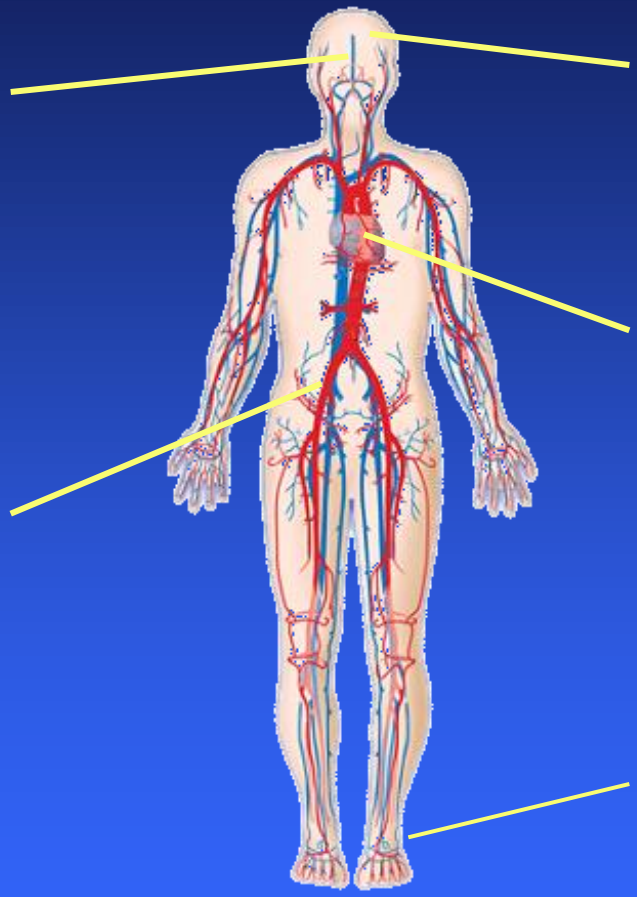
Diabetic retinopathy

Leading cause of blindness in working-age adults[1]



Diabetic nephropathy

Leading cause of end-stage renal disease[2]





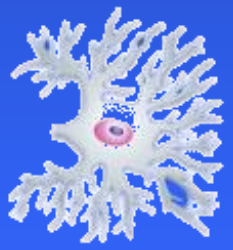
Stroke

1.2 to 1.8-fold increase in stroke[3]



Cardiovascular disease

75% diabetic patients die from CV events[4]



Diabetic neuropathy

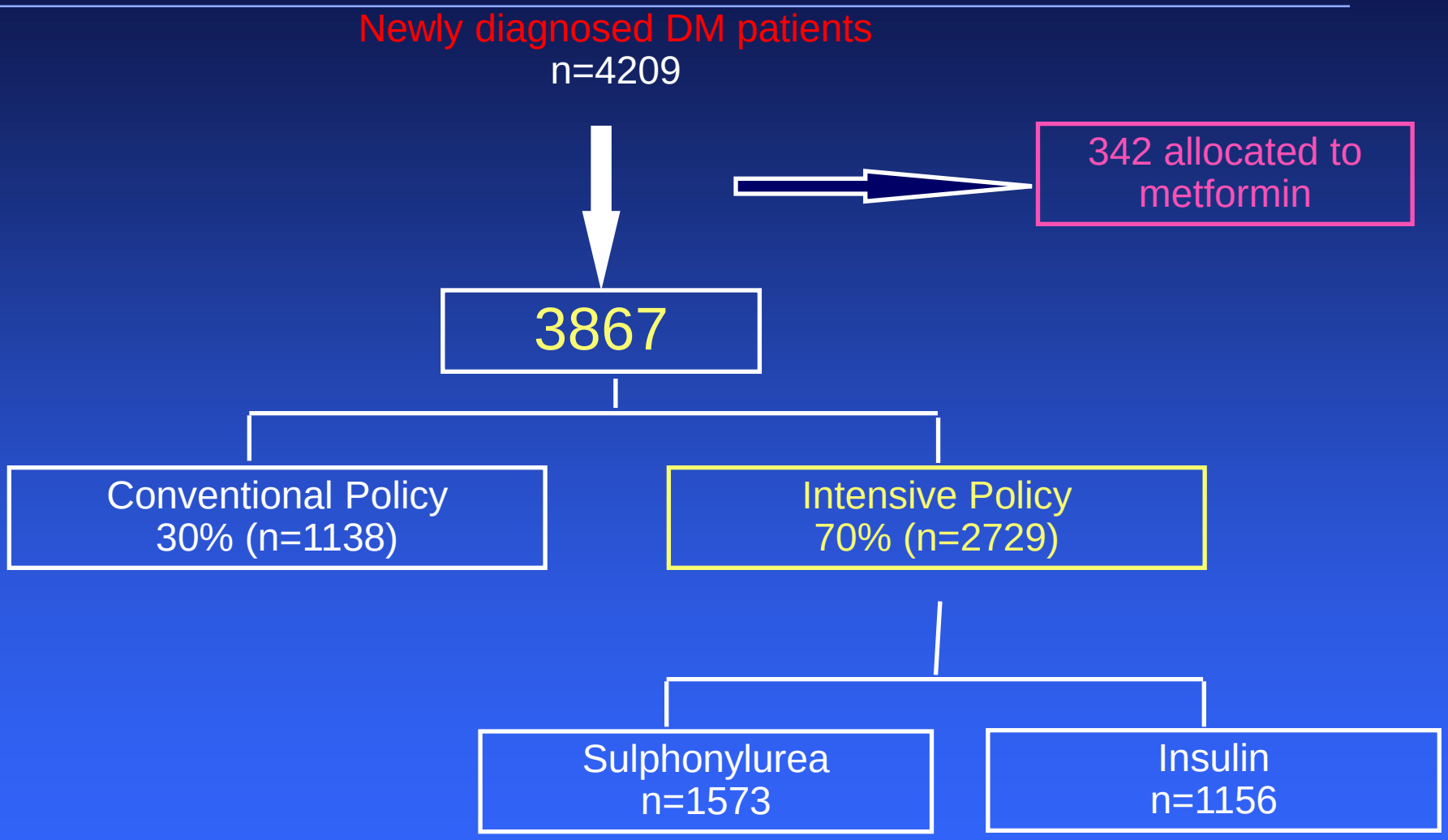
Leading cause of non-traumatic lower extremity amputations[5]

[1]Fong DS, *et al. Diabetes Care* 2003;26(Suppl. 1):S99–S102. [2]Molitch ME, *et al. Diabetes Care* 2003;26(Suppl. 1):S94–S98. [3]Kannel WB, *et al*. *Am Heart J* 1990;120:672–676. [4]Gray RP & Yudkin JS. In *Textbook of Diabetes* 1997. [5]Mayfield JA, *et al. Diabetes Care* 2003;26(Suppl. 1):S78–S79.

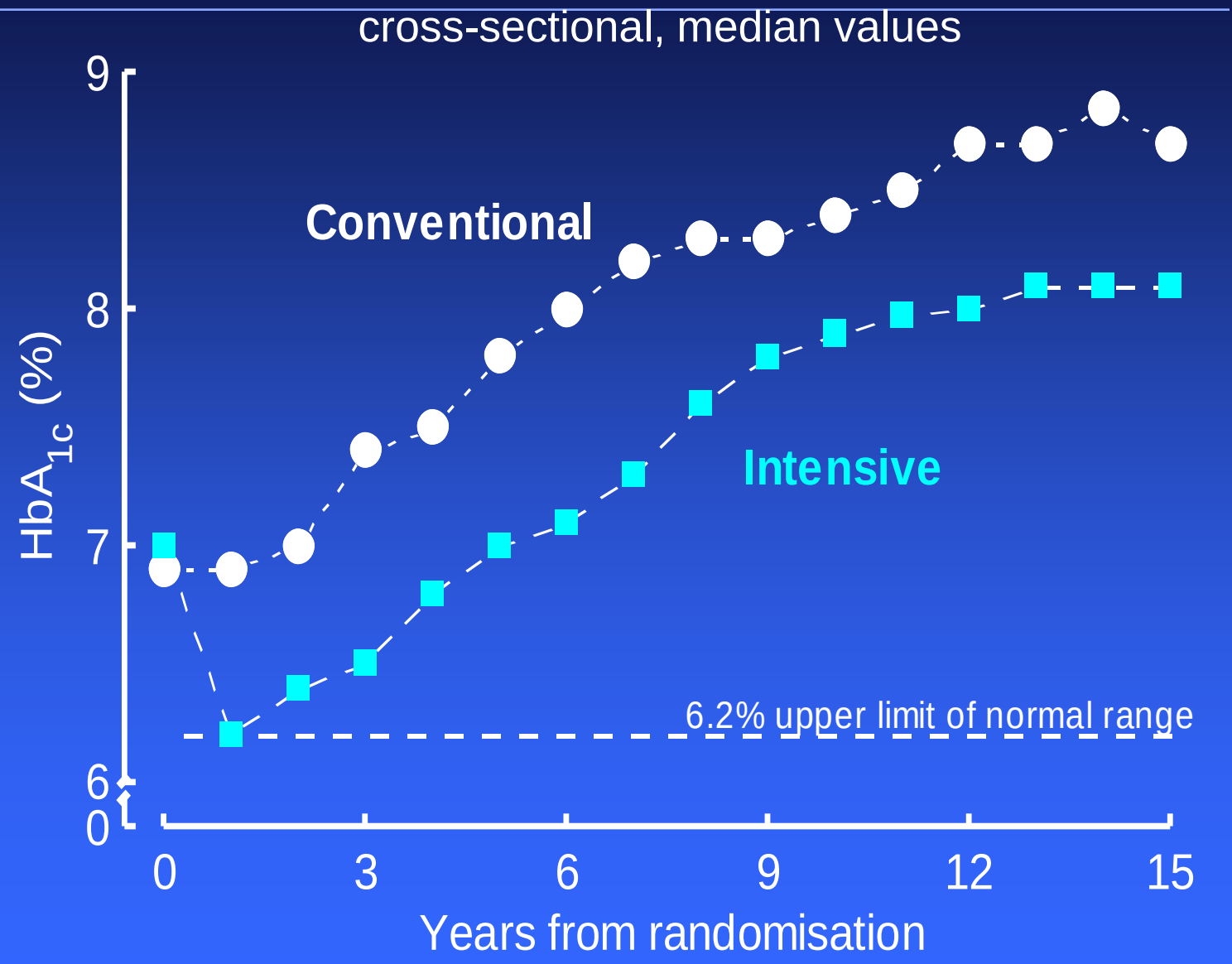
Determine the optimal HbA1c – Insights from the latest randomized trials



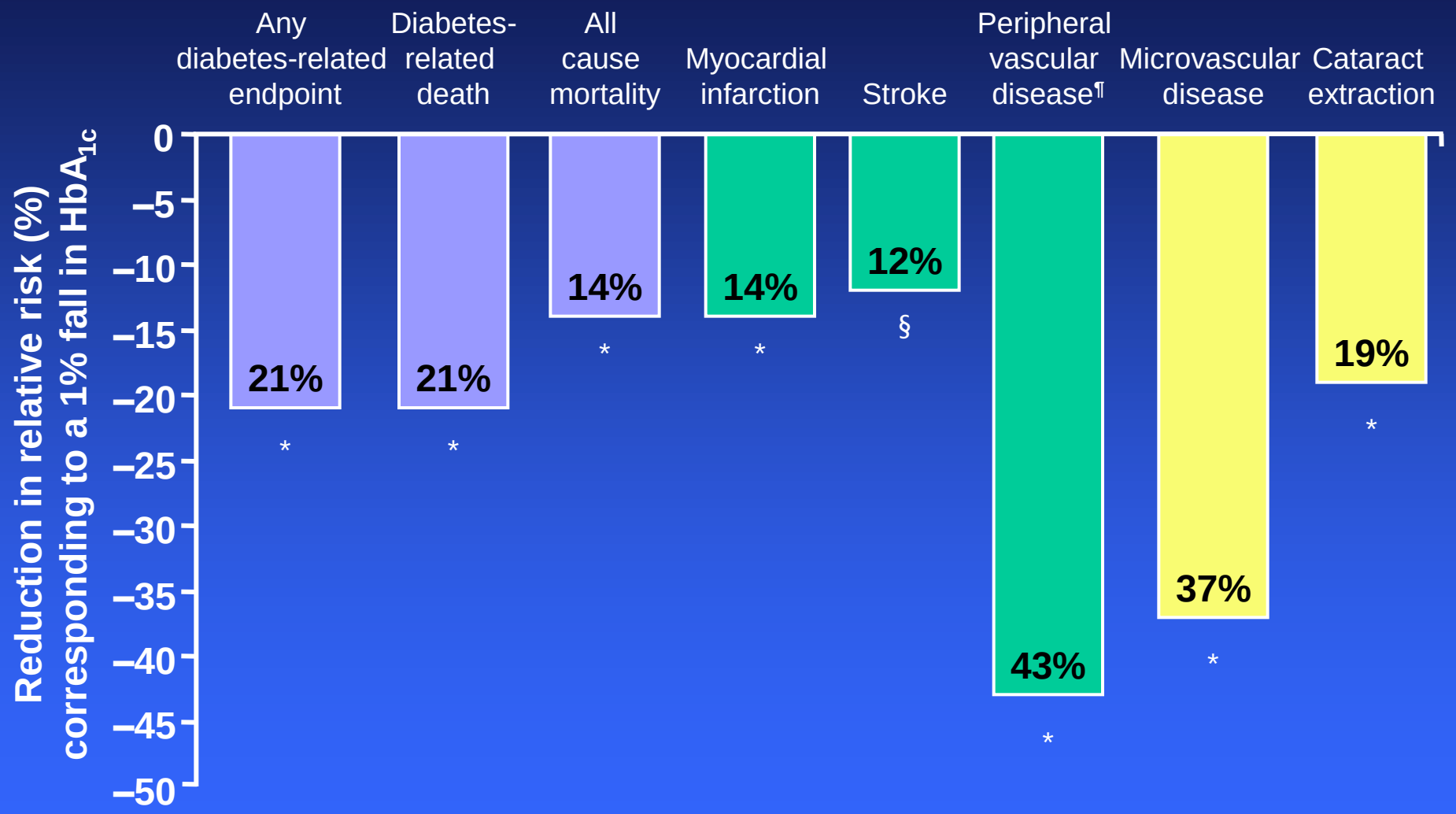
UKPDS


Newly diagnosed DM patients
n=4209
342 allocated to metformin
3867
Conventional Policy
30% (n=1138)
Intensive Policy
70% (n=2729)
Sulphonylurea
n=1573
Insulin
n=1156

HbA_{1c}


cross-sectional, median values
9
8
7
6
0
HbA_{1c} (%)
Conventional
Intensive
6.2% upper limit of normal range
0
3
6
9
12
15
Years from randomisation

UKPDS: A 1% fall in HbA_{1c} results in a reduction of relative risk of complications

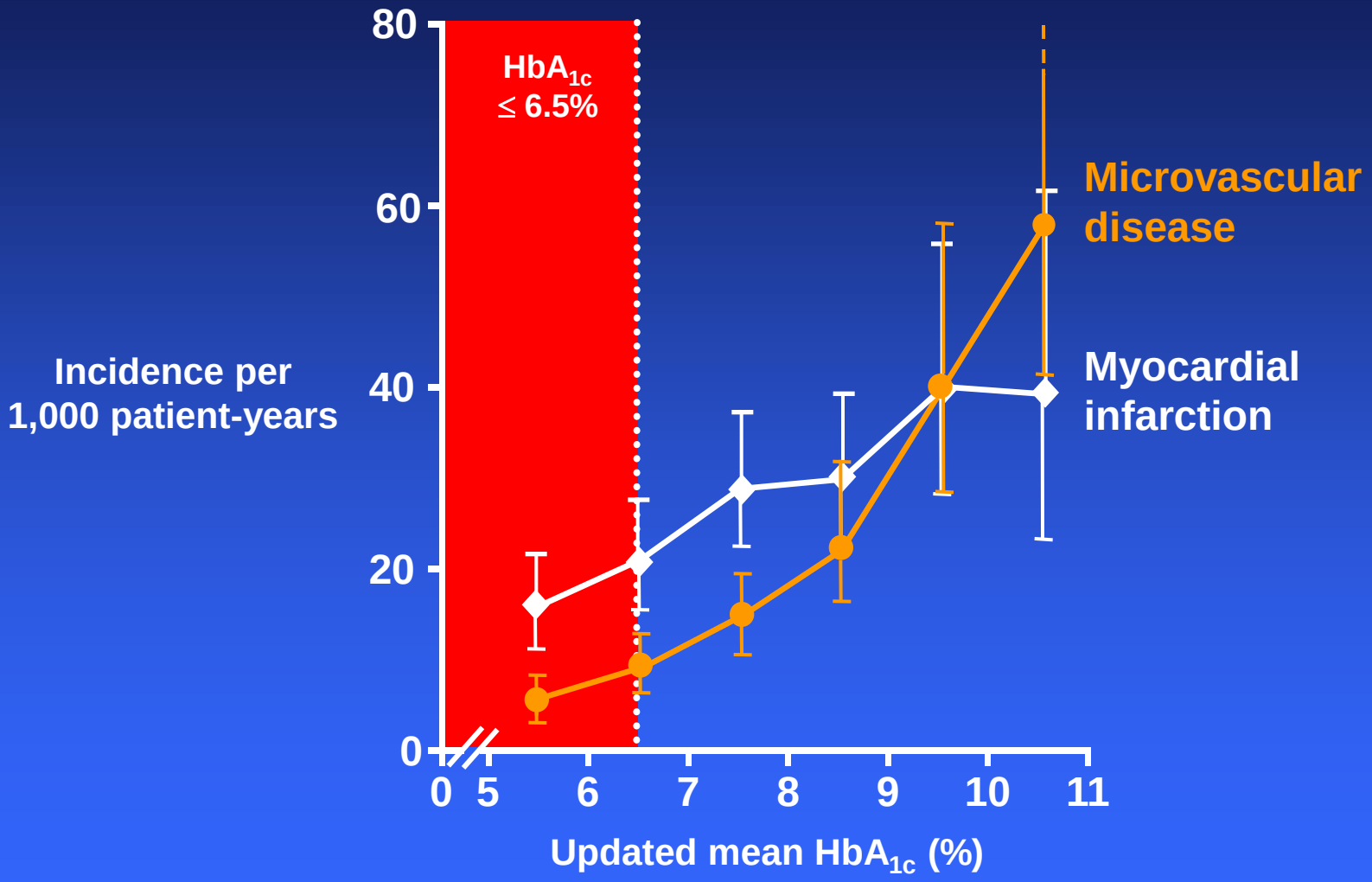


*P < 0.0001 versus baseline; §P = 0.035

¶Lower extremity amputation or fatal peripheral vascular disease

Adapted from Stratton IM, *et al.* UKPDS 35. *BMJ* 2000;321:405–412.

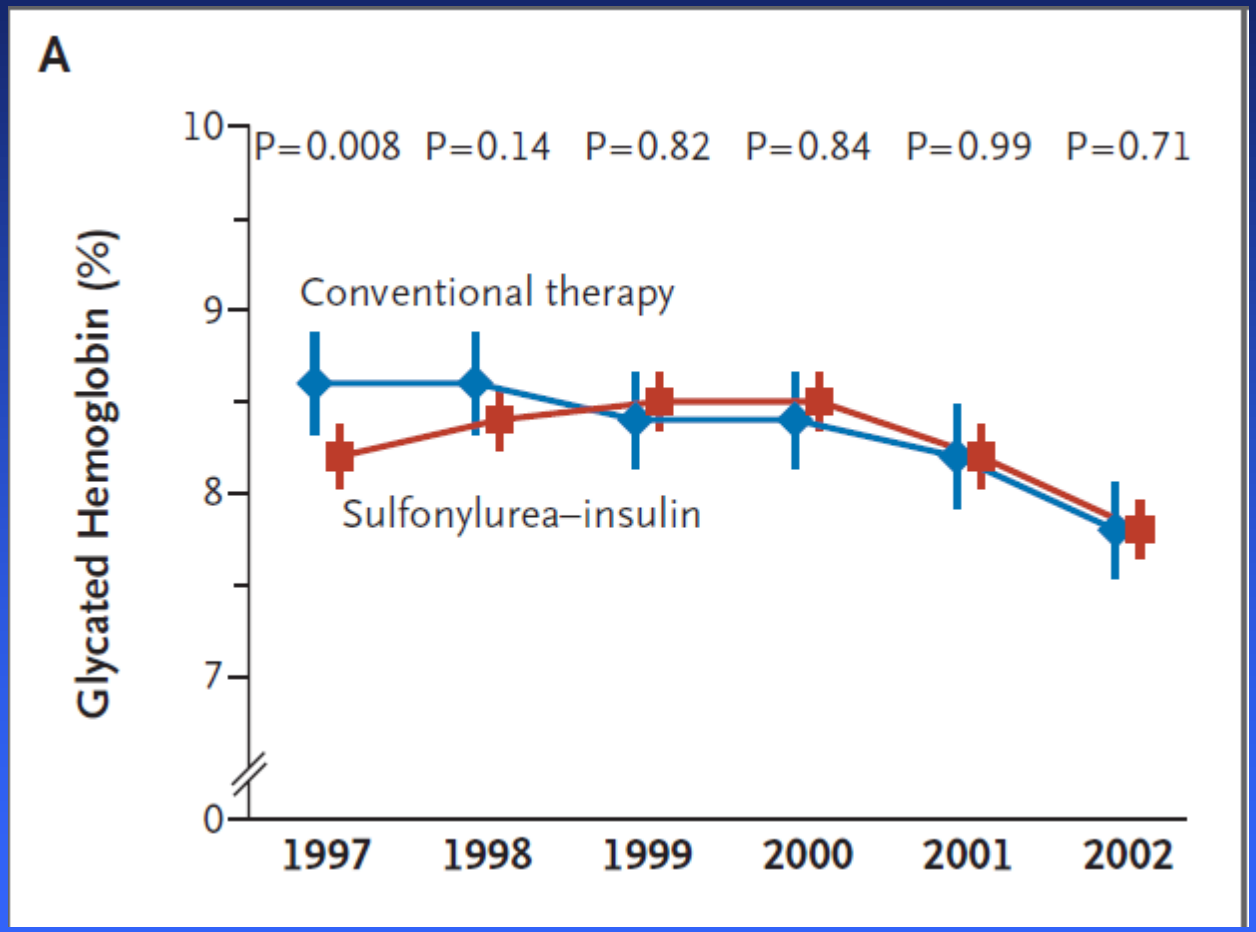
UKPDS: Elevated blood glucose levels increase the risk of diabetic complications



Study population: White, Asian Indian and Afro-Caribbean UKPDS patients (n = 4,585)
Adjusted for age, sex and ethnic group
Error bars = 95% CI

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

UKPDS – 10 year follow up study



Between group differences in HbA1c were lost after the first year

N Engl J Med 359:15 Oct 9, 2008

UKPDS – 10 year follow up study

- In the sulphonylurea-insulin group

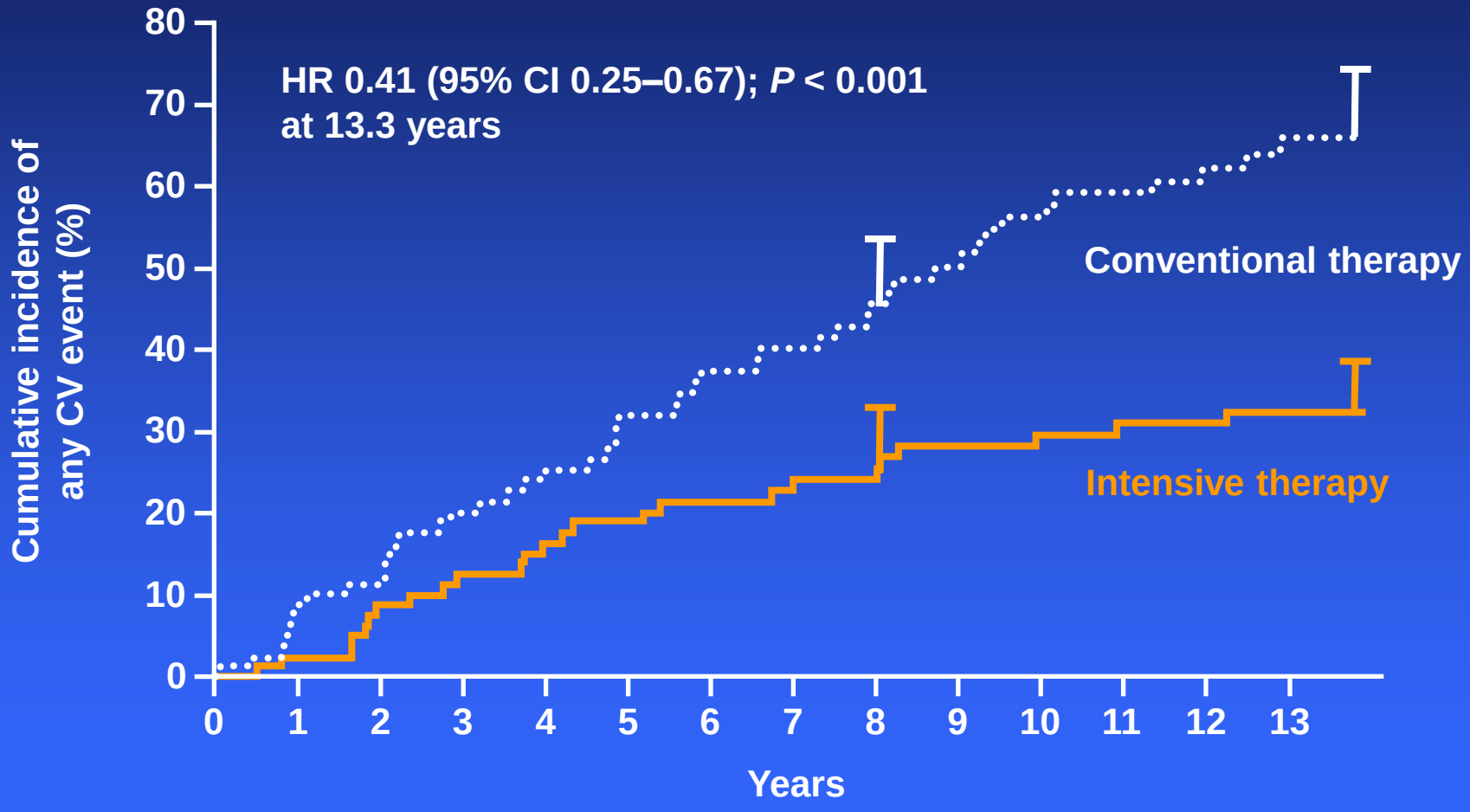
	Relative risk reduction
Any DM related end-point	9% (p= 0.04)
Microvascualr disease	24% (p=0.001)
Myocardial infarction	15% (p=0.01)
Death from any cause	13% (p= 0.007)

- In the metformin group

	Relative risk reduction
Any DM related end-point	21% (p= 0.01)
Myocardial infarction	33% (p=0.005)
Death from any cause	27% (p= 0.002)

N Engl J Med 359:15 Oct 9, 2008

Steno-2: Intensive multifactorial therapy associated with improved outcomes



Adapted from Gaede P, *et al*. *N Engl J Med* 2008;358:580–591.

HbA1c: Is lower always better?



ACCORD: Action to Control Cardiovascular Risk in Diabetes

Primary objective: To determine if CVD event rates can be reduced by targeting hyperglycaemia, hypertension and dyslipidaemia

Patient population: Type 2 diabetes at high risk of CV event (N = 10,251; mean age 62)

Primary end point: First occurrence of major CVD event (non-fatal MI, non-fatal stroke or CV death)

	Intensive glycaemic control (HbA_{1c} <6.0%)	Standard glycaemic control (HbA_{1c} 7.0–7.9%)	Difference
Deaths, n	257	203	54
Rate per 1,000 patients/year	14	11	3

Average duration of treatment ~ 4 years. Intensive glycaemic control arm stopped 18 months early by DSMB and patients switched to standard glycaemic control

ACCORD Study Group. *Am J Cardiol* 2007;99:21i–33i. NHLBI. http://public.nhlbi.nih.gov/newsroom/home/GetPressRelease.aspx?id=2551 (accessed 23 February 2008)

ADVANCE: Action in Diabetes and Vascular disease: Preterax and Diamicron-MR Controlled Evaluation

Primary objective: To determine the effect of BP (ACE-inhibitor + diuretic versus placebo) and glycaemic (intensive versus standard) intervention on micro- and macrovascular complications in patients with T2DM (2 x 2 factorial design)

Patient population: Type 2 diabetes (hypertensive + non-hypertensive) (N = 11,140)

Glycaemic control	Blood pressure intervention	
Intensive* (HbA_{1c} ≤6.5%)	Perindopril + indapamide	Placebo
Standard¶	Perindopril + indapamide	Placebo

*Gliclazide plus oral agents/insulin to achieve HbA_{1c} target; ¶Based on standard guidelines

Primary end point: Macrovascular: composite of non-fatal stroke, non-fatal MI, CV death
Microvascular: composite of new or worsening nephropathy or retinopathy

Secondary end points: Cerebrovascular disease, CVD, PVD, microalbuminuria, visual deterioration, neuropathy, heart failure, cognitive function and dementia, all-cause mortality

Treatment duration: 4.5 years

ADVANCE Management Committee. *Diabetologia* 2001;44:1118–1120.

ADVANCE results

After a median of 5 years of follow-up:

- Mean HbA1c level was lower in the intensive-control group (6.5%) than in the standard-control group (7.3%).

- Intensive control reduced the incidence of:
  - combined major macrovascular and microvascular events (18.1%, versus 20.0% with standard control; hazard ratio, 0.90; 95% confidence interval [CI], 0.82 to 0.98; *P* = 0.01)
  - major microvascular events (9.4% versus 10.9%; hazard ratio, 0.86; 95% CI, 0.77 to 0.97; *P* = 0.01), primarily because of a reduction in the incidence of nephropathy (4.1% versus 5.2%; hazard ratio, 0.79; 95% CI, 0.66 to 0.93; *P* = 0.006), with no significant effect on retinopathy (*P* = 0.50)

- There were no significant effects of the type of glucose control on major macrovascular events, death from cardiovascular causes, or death from any cause

ADVANCE Collaborative Group. *N Engl J Med* 2008;358:2560–2572.

What Are Potential Explanations for Increased CVD Death With Intensive Glycemic Control in ACCORD?

- Post hoc analyses have been unable to prove or disprove causes of increased CVD death with intensive glycemic control
- Randomization to the intensive arm was associated with or led to many downstream effects
  - Higher rates of severe hypoglycemia
  - More frequent use of insulin, TZDs
  - Greater weight gain

Skyler JS et al. *J Am Coll Cardiol.* 2009;53:298-304.

- It is likely that the increase in mortality in ACCORD was related to the overall treatment strategies for intensifying glycemic control
    - Not attributed to the achieved A1C
- ADVANCE achieved a median A1C in the intensive arm similar to that in ACCORD, with no increased mortality hazard
- Thus, the ACCORD mortality findings do not imply that patients with T2DM who can easily achieve or maintain low A1C levels with lifestyle modifications with or without pharmacotherapy are at risk and need to “raise” their A1C

Skyler JS et al. *J Am Coll Cardiol.* 2009;53:298-304.

VADT: Veteran Affairs Diabetes Trial

Primary objective: To evaluate the effect of intensive ($HbA_{1c} \leq 6\%$) versus standard (HbA_{1c} 8–9%) glycaemic control* on CV events in type 2 diabetes

Patient population: Type 2 diabetes (N = 1,792)



Primary endpoint: Occurrence of any major CV event: MI, stroke, new or worsening CHF, amputation for ischemic diabetic gangrene, invasive intervention for CAD or PVD, CV death

Secondary endpoints: Additional CV end points (new or worsening angina, new transient ischemic attacks, new intermittent claudication, new critical limb ischemia, total mortality), microvascular complications, cost, QoL

Treatment duration: 5–7 years

*To achieve glycaemic targets, both study arms received stepwise treatment with glimepiride or metformin plus rosiglitazone followed by the addition of insulin, with the addition of other oral agents, as needed

Abraira C, *et al. J Diabet Complications* 2003;17:314–322.

VADT: Key results

- The primary result of VADT did not show that intensive blood sugar control (HbA1c levels below 7%) had a statistically significant effect on reducing major CV events associated with diabetes
- In standard group:
- Worsening of albumin excretion was greater (p= 0.01)
- Progression to macroalbuminuria was greater (p=0.04)

ADA guideline

- Concerning ACCORD, ADVANCE, VADT

1. No significant reduction in CVD outcomes with intensive glycemic control in these populations, who had more advanced diabetes than UKPDS participants
2. All three of these trials were conducted in participants with more-long-standing diabetes (mean duration 8 – 11 years)
3. With known CVD or multiple cardiovascular risk factor

Glycemic targets

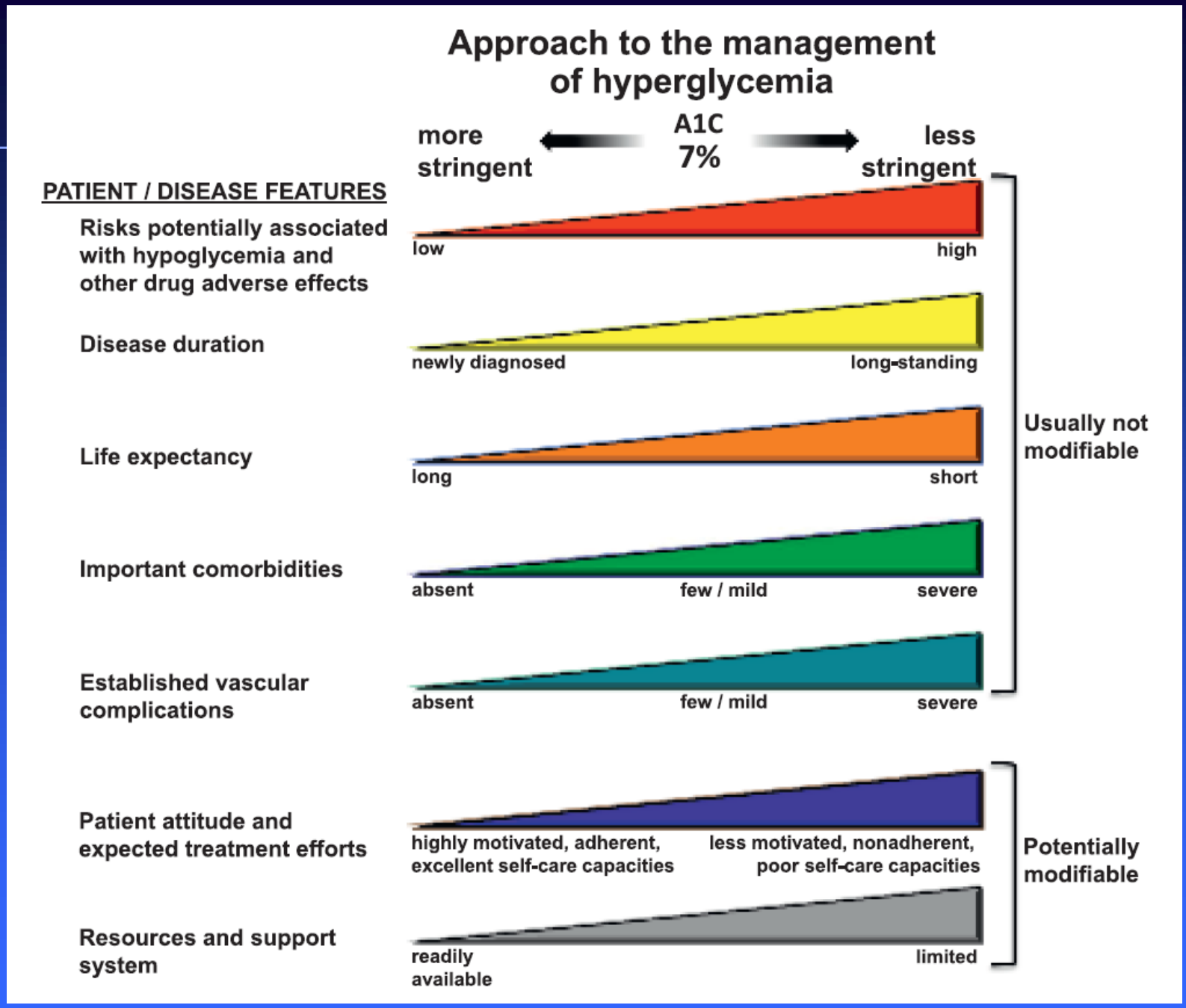
Table 5.2—Summary of glycemic recommendations for nonpregnant adults with diabetes

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)

*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.

2016 ADA guideline



2016 ADA guideline

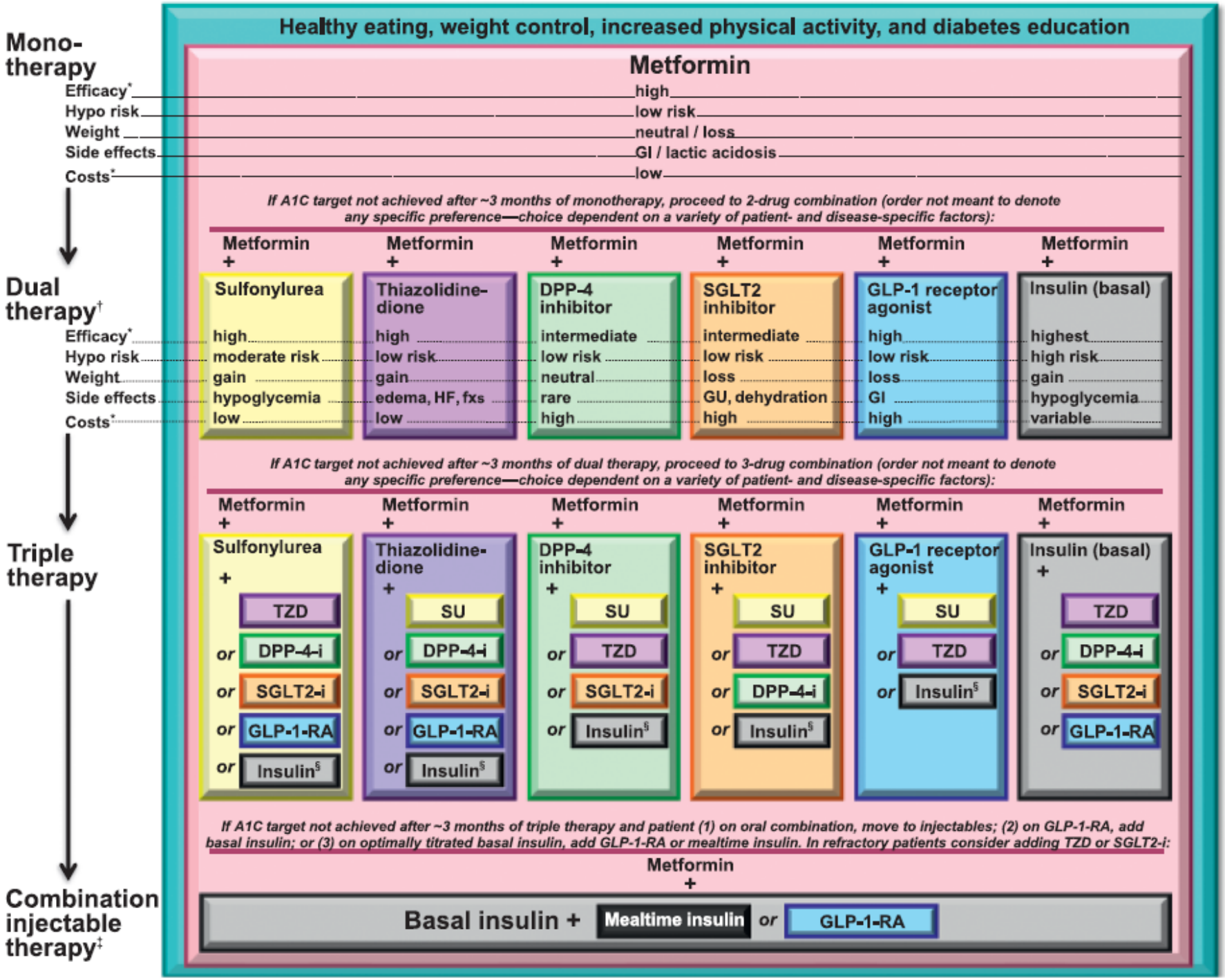
Near normal glycemic targets

- Younger patients
- Recent onset of type 2 diabetes mellitus
- Little or no micro- or macrovascular complications
- With the aim of preventing complications over the many years of life



Annals of Internal Medicine. Issue: Volume 154(8), 19 April 2011, pp 554-559

Treatment algorithm


Healthy eating, weight control, increased physical activity, and diabetes education
Mono-therapy
Metformin
Efficacy* high
Hypo risk low risk
Weight neutral / loss
Side effects GI / lactic acidosis
Costs* low
If A1C target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):
Dual therapy†
Metformin + Sulfonylurea
Efficacy* high
Hypo risk moderate risk
Weight gain
Side effects hypoglycemia
Costs* low
Metformin + Thiazolidine-dione
high
low risk
gain
edema, HF, fxs
low
Metformin + DPP-4 inhibitor
intermediate
low risk
neutral
rare
high
Metformin + SGLT2 inhibitor
intermediate
low risk
loss
GU, dehydration
high
Metformin + GLP-1 receptor agonist
high
low risk
loss
GI
high
Metformin + Insulin (basal)
highest
high risk
gain
hypoglycemia
variable
If A1C target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):
Triple therapy
Metformin + Sulfonylurea + TZD or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin§
Metformin + Thiazolidine-dione + SU or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin§
Metformin + DPP-4 inhibitor + SU or TZD or SGLT2-i or Insulin§
Metformin + SGLT2 inhibitor + SU or TZD or DPP-4-i or Insulin§
Metformin + GLP-1 receptor agonist + SU or TZD or Insulin§
Metformin + Insulin (basal) + TZD or DPP-4-i or SGLT2-i or GLP-1-RA
If A1C target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:
Combination injectable therapy‡
Metformin +
Basal insulin + Mealtime insulin or GLP-1-RA

Oral Anti-Diabetic drugs (OAD)

Insulin Secretagogues

Stimulate endogenous insulin secretion

(I) Sulphonylureas (SU)

- Reduce HbA1c by 1.5%
- S/E: Encourage weight gain, risk of hypoglycemia
- β-cell exhaustion over long-term exposure

(I) Sulphonylurea (SU)

First generation

- Tobutamide
- Chlorpropamide

Second generation

- Daonil- caution in elderly, liver and renal failure because of risk of hypoglycemia
- Diamicron / Minidiab - Shorter duration of action, metabolized mainly by liver

**1st generation and Daonil are out of favor nowadays

(I) Sulphonylurea (SU)

Third generation

Glimepiride (Amaryl)

-It stimulates insulin release from pancreas but different binding sites at the ß-cell

-Rapid onset of action but long duration of action

Oral Anti-Diabetic drugs (OAD)

Insulin Sensitizers

Biguanides (Metformin: Glucophage)

- First line treatment
- Reduce HbA1c by 1.5%
- Inhibition of hepatic gluconeogenesis
- Not cause hypoglycemia when used alone
- Some weight loss in most patients
- Decrease cardiovascular events in several studies
- Dosage: 500mg to 3g daily in BD or TDS
- S/E:GI upset (can be minimized by starting with low dose)

(I) Biguanides

Risk of lactic acidosis, should not be given :

- Renal insufficiency, serum creatinine >150μmol/L
- Heart failure
- Concurrent liver disease
- Severe infection with ↓ tissue perfusion
- Hypoxic states
- Serious acute illness

Oral Anti-Diabetic drugs (OAD)

Insulin Sensitizers

(II) Thiazolidindiones (TZD)

- PPAR-γ agonist
- Reduce HbA1c by 0.8-1.0%
- Increase insulin sensitivity and glucose uptake by skeletal muscles, ↓ hepatic insulin resistance

(II) Thiazolidindiones (TZD)

Rosiglitazone

- Reported a 1.4 fold ↑in risk of acute MI compared with non-thiazolidinedione

  (Nissen S E et al. NEJM 2007)

- In HK, all drug containing rosiglitazone were withdrawn from market since September 2010

(II) Thiazolidindiones (TZD)

Pioglitazone (Actos)

- Dose: 15-45mg daily
- The use of pioglitazone > 2 years is associated with ↑risk of CA bladder (Lewis J D et al. *Diabetes Care*.2011; 34: 916-22)
- S/E: Weight gain, fluid retention, heart failure especially combined with insulin, hepatotoxicity, ↓haematocrit, ↑incidence of # in female patients

(II) Thiazolidindiones (TZD)

Pioglitazone (Actos)

TZD is contraindicated in:

- NYHA Class III to IV HF
- Liver derangement, ALT >2.5 upper limit of normal
- Hx. of ACS

(II) Thiazolidindiones (TZD)

Pioglitazone (Actos)

Current FDA recommendation on pioglitazone:

- Do not use in patients with active CA bladder
- Use with caution in patients with prior Hx. Of CA bladder
- Counsel patients to report any S/S of blood in the urine, urinary urgency, pain on urination, or back / abdominal pain as these may be due to bladder cancer

Oral Anti-Diabetic drugs (OAD)

Alpha-Glucosidase inhibitors

Acarbose (Glucobay)

- Reduction of post prandial hyperglycemia by delaying carbohydrate absorption
- Reduction of HbA1c by 0.5-0.8%
- Dose: 50-100mg TDS
- Expensive, mild potency
- S/E: GI upset

Alpha-Glucosidase inhibitors

Acarbose (Glucobay)

- Abnormal liver function test have been reported in patients taking high dosage e.g. 300mg TDS
- Must be taken with the first or second mouthful of food for optimal effects
- C/I: Inflammatory bowel disease

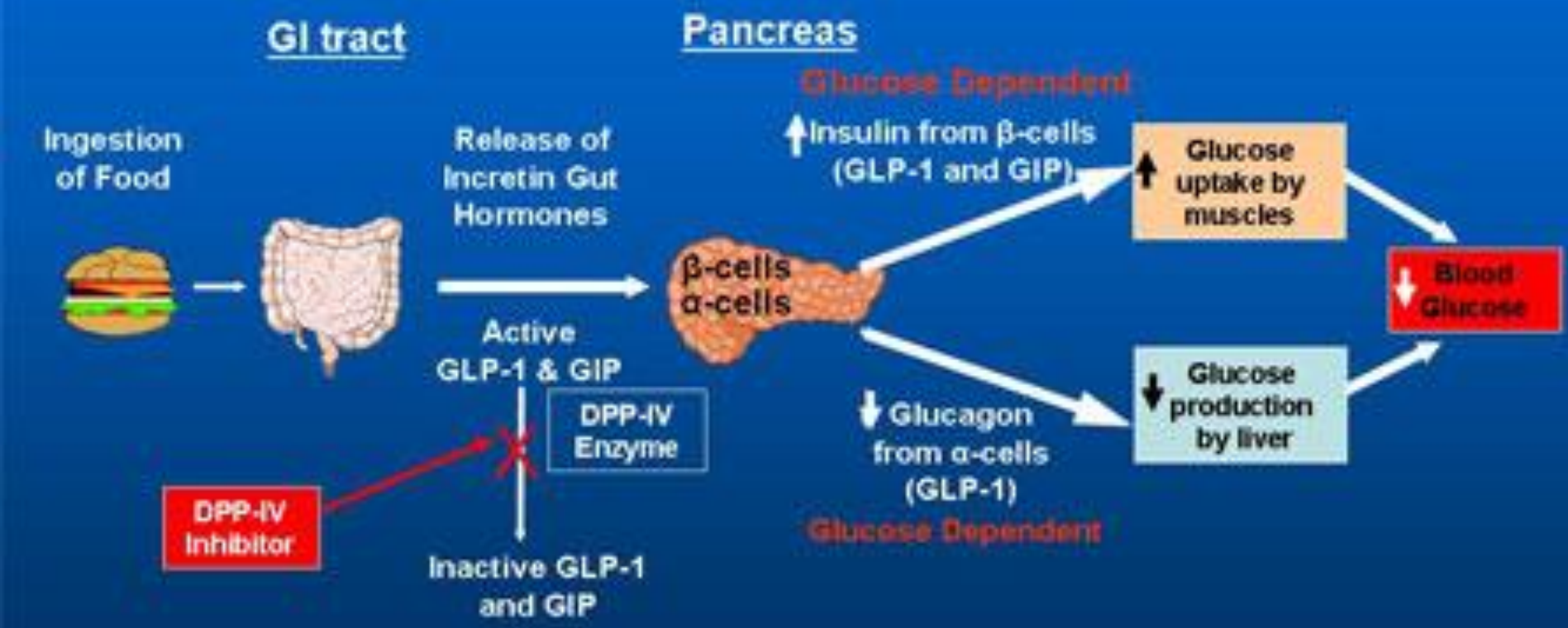
Oral Anti-Diabetic drugs (OAD)

Dipeptidylpeptidase-IV (DPP-IV) inhibitors

1. **Sitagliptin (Januvia)**
2. **Vildagliptin (Galvus)**
3. **Saxagliptin (Onglyza)**
4. **Linagliptin (Tradjenta)**
5. **Alogliptin (Nesina)**

- Inhibition of degradation of endogenous GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) with ↑ meal-stimulated insulin levels

DPP-IV Inhibitors: Physiologic Action



DPP-IV inhibitors

- Reduction of HbA1c by 0.5-0.9%
- Low incidence of hypo. if used alone, well tolerated
- S/E: Upper respiratory infection, Headache, nasopharyngitis

HA Formulary

- Alternative to insulin after failure of optimal doses of SU & metformin
- Discontinue if HbA1c still >8% within 6-8 months

- During postmarketing surveillance, acute pancreatitis was reported in 88 patients taking sitagliptin between October 2006 and February 2009
- In 19 of the 88 reported cases (21%), pancreatitis occurred within 30 days of starting sitagliptin
- A causative relationship between sitagliptin and pancreatitis has not been established.

- ? increased hospitalization rate of heart failure

1. SAVOR-TIMI 53 trial: for heart failure in saxagliptin group (Hazard ratio 1.27: 95% CI1.07 to 1.51)
2. EXAMINE trial: non-significant increase in alogliptin group (Hazard ratio 1.18: 95% CI 0.90 to 1.58)

Egan AG, Blind E, Dunder K, et al. 2014)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes

Jennifer B. Green, M.D., M. Angelyn Bethel, M.D., Paul W. Armstrong, M.D., John B. Buse, M.D., Ph.D., Samuel S. Engel, M.D., Jyotsna Garg, M.S., Robert Josse, M.B., B.S., Keith D. Kaufman, M.D., Joerg Koglin, M.D., Scott Korn, M.D., John M. Lachin, Sc.D., Darren K. McGuire, M.D., M.H.Sc., Michael J. Pencina, Ph.D., Eberhard Standl, M.D., Ph.D., Peter P. Stein, M.D., Shailaja Suryawanshi, Ph.D., Frans Van de Werf, M.D., Ph.D., Eric D. Peterson, M.D., M.P.H., and Rury R. Holman, M.B., Ch.B., for the TECOS Study Group*

N ENGL J MED 373;3 NEJM.ORG JULY 16, 2015

Objective: to study the long-term effect on cardiovascular events of adding sitagliptin, a DPP4 inhibitor, to usual care in patients with type 2 DM and cardiovascular disease

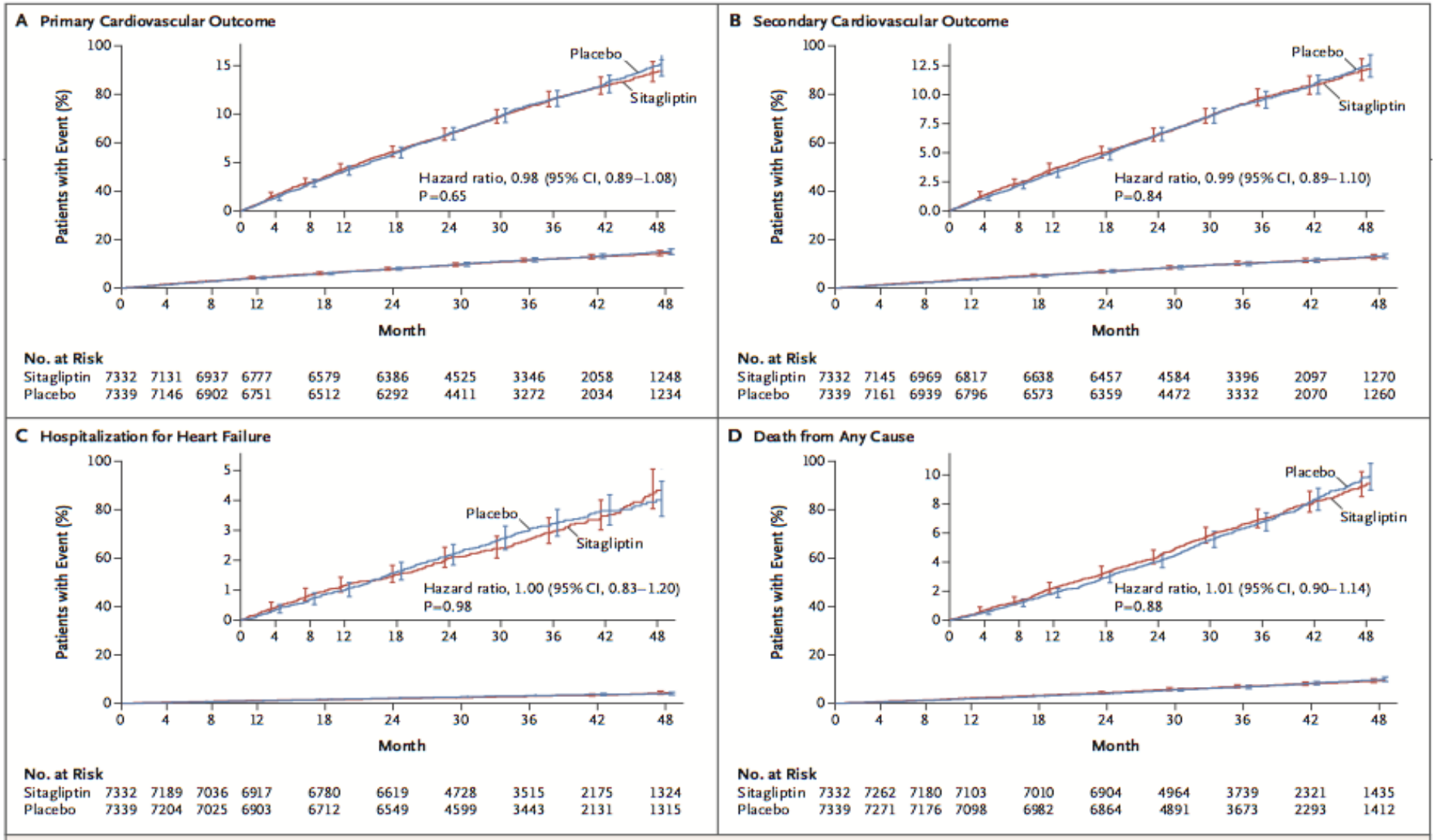


Figure 3. Kaplan–Meier Curves for Primary and Secondary Outcomes (Intention-to-Treat Population).

Shown are the rates of the primary cardiovascular outcome (a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina) (Panel A), the secondary cardiovascular outcome (a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) (Panel B), hospitalization for heart failure (Panel C), and death from any cause (Panel D) in the sitagliptin and placebo groups. The inset graph in each panel shows the same curves on a larger scale. The I bars indicate 95% confidence intervals.

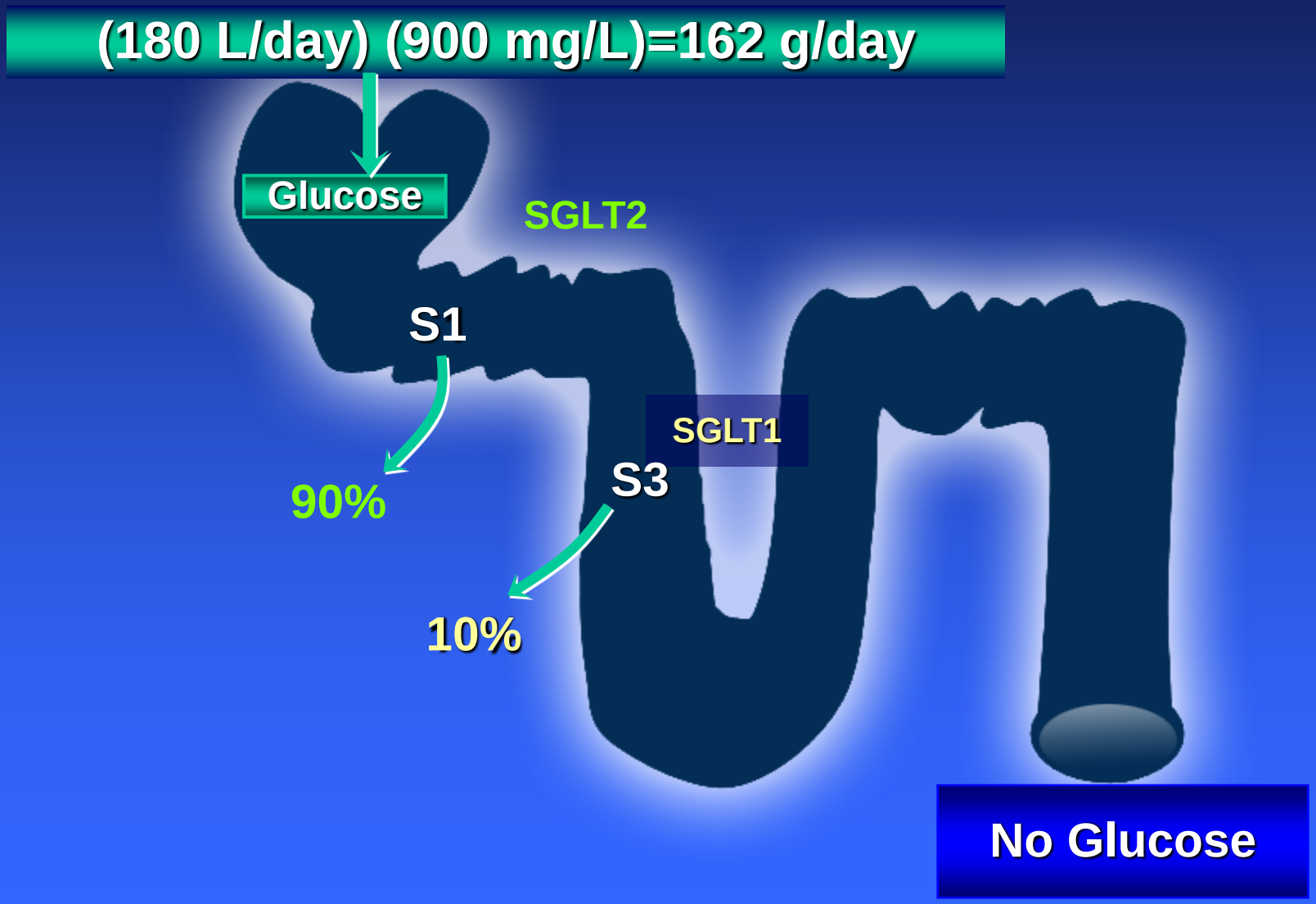
SGLT 2 inhibitors

- Sodium-glucose cotransporter 2 (SGLT2) plays a role in renal glucose reabsorption in proximal tubule
- Renal glucose reabsorption is increased in type 2 diabetes
- Selective inhibition of SGLT2 increases urinary glucose excretion, reducing blood glucose

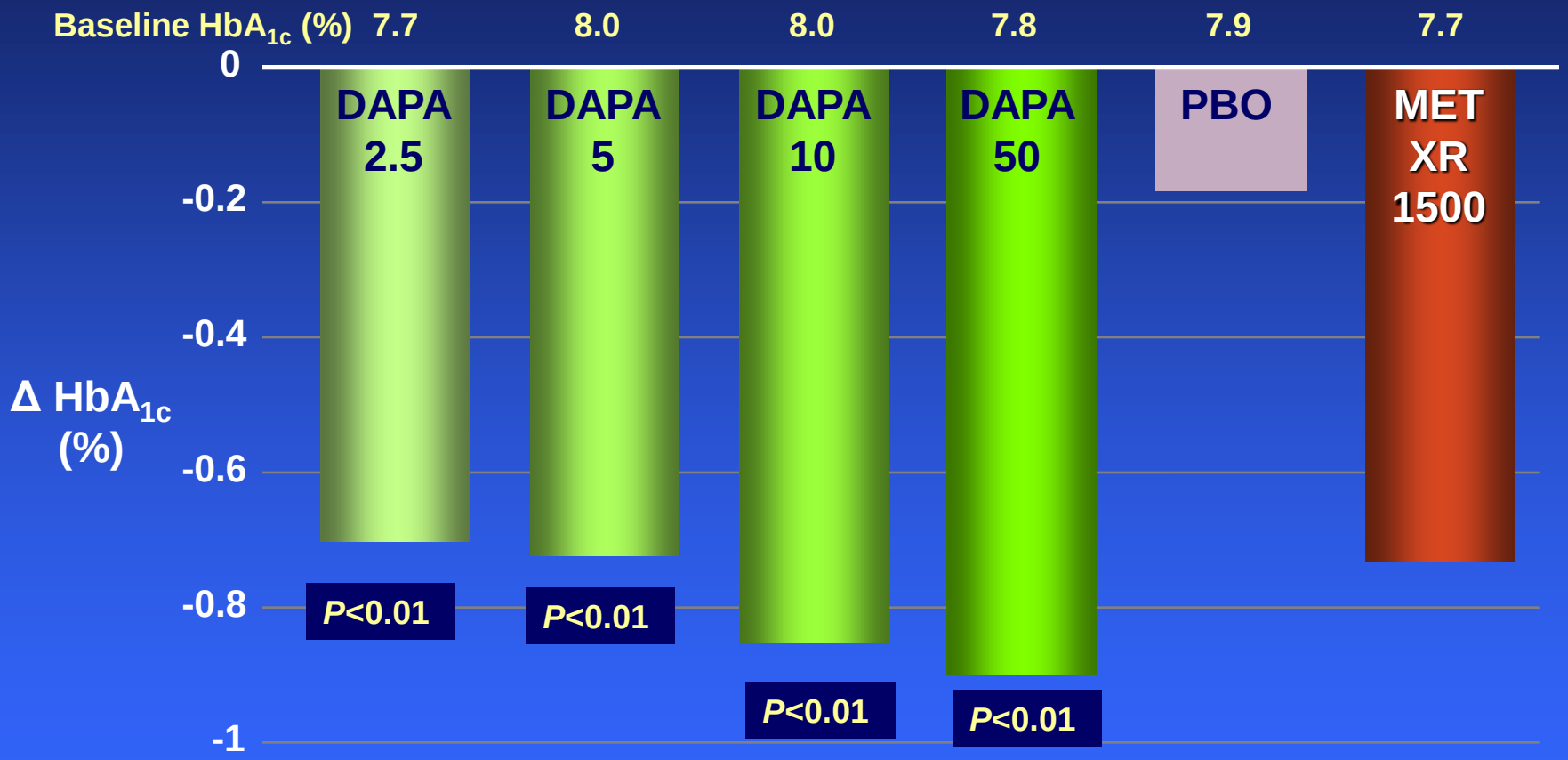
Wright EM, et al. *J Intern Med*. 2007;261:32-43.

- Canagliflozin
- Dapagliflozin
- Emgapliflozin

Renal Handling of Glucose



Effect of Dapagliflozin on HbA_{1c}



All comparisons vs placebo; no statistical comparisons with metformin were made.

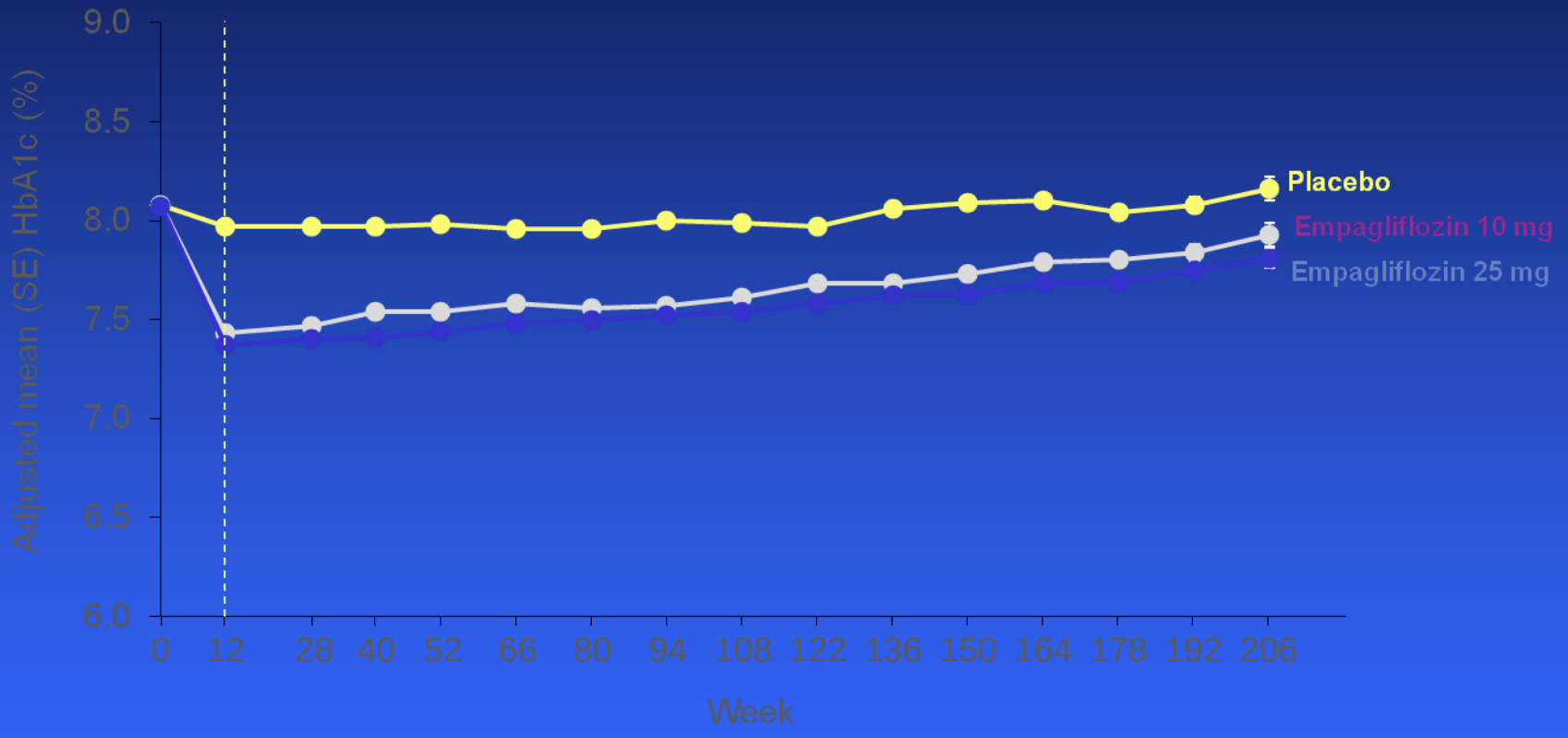
List JF, et al. *Diabetes Care*. 2008;2009;32:650-657.

Empagliflozin

- In patients with type 2 diabetes, empagliflozin leads to:
  - Significant reductions in HbA1c
  - Weight loss
  - Reductions in blood pressure without increases in heart rate

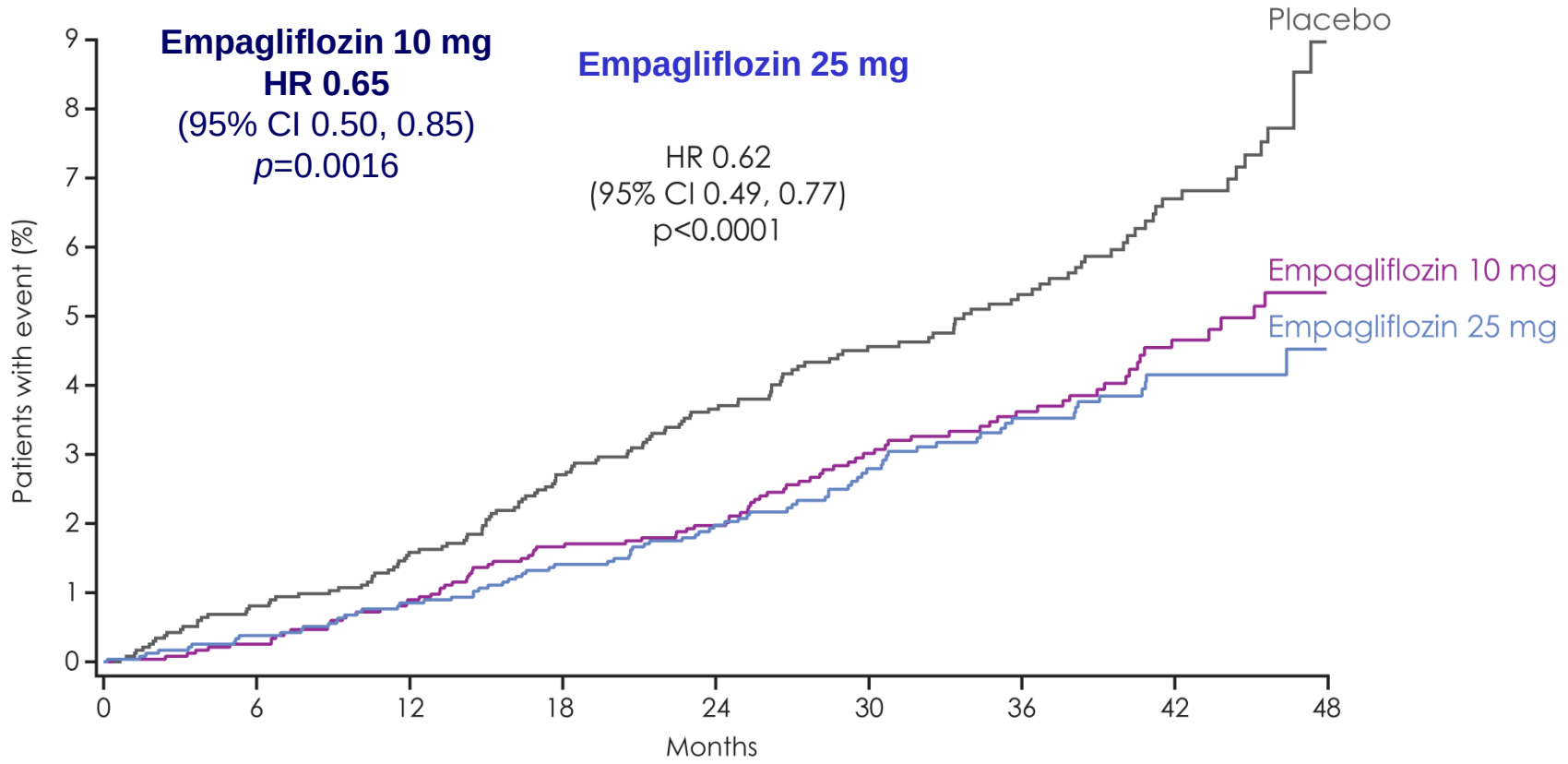
Liakos A et al. Diabetes Obes Metab 2014;16:984-93

HbA1c



Placebo	2294	2272	2188	2133	2113	2063	2008	1967	1741	1456	1241	1109	962	705	420	151
Empagliflozin 10 mg	2296	2272	2218	2150	2155	2108	2072	2058	1805	1520	1297	1164	1006	749	488	170
Empagliflozin 25 mg	2296	2280	2212	2152	2150	2115	2080	2044	1842	1540	1327	1190	1043	795	498	195

CV death



No. of patients									
Empagliflozin 10 mg	2345	2327	2305	2274	2055	1542	1303	847	201
Empagliflozin 25 mg	2342	2324	2303	2282	2073	1537	1314	875	213
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Cumulative incidence function. HR, hazard ratio

Incretin mimetic

Incretin mimetic

Glucagon like peptide 1 (GLP-1) analogues

- A lizard derived GLP-1 receptor agonist
- Stimulate glucose-dependent insulin release
- Suppress glucagon & ↓gastric emptying
- Prevent β-apoptosis and may restore β-cell mass (Animal data)

Exenatide (Byetta)

Liraglutide (Victoza)

Lixisenatide (Lyxumia)

Incretin mimetic

- Consider using in obese patients with type 2 DM on maximal OAD but do not achieve HbA1c target (Used in combination with metformin &/ or SU)
- Hypoglycemia rare, weight loss in most patients
- S/E: GI upset (nausea and vomiting, risks of pancreatitis)
- Dose: Subcutaneous injection twice daily before main meals
- Eat within the first hour following injection

Insulin

Insulin secretion:-

Continuous basal insulin secretion

- Restrains hepatic glucose production
- Keeping it in equilibrium with basal glucose utilization by brain and other tissue

Incremental prandial insulin secretion

- Stimulates glucose utilization
- Inhibits hepatic glucose output
- Glucose storage

Type of insulin

(1) Very rapid acting (Clear solution)

Insulin Lispro (Humalog from Lily)

Insulin Aspart (Novorapid from Novo Nordisk)

- Insulin analogues obtained by recombinant DNA technology
- Rapid onset of action and short duration
- Control post prandial glucose better than regular insulin and cause less hypo.
- Given immediately before meals

Type of insulin

(2) Short acting (Neutral regular insulin- clear)

Humulin R (Lily)

Actrapid (Novo Nordisk)

(3) Intermediate acting (NPH, Human Insulin Isophane Suspension- Cloudy)

Humulin N (Lily)

Protaphane (Novo Nordisk)

Type of insulin

(4) Long acting (Clear solution)

Insulin Glargine (Lantus from Sanofi Adventis)

Insulin Detemir (Levemir from Novo Nordisk)

- Insulin analogues
- Provide a constant basal insulin level over 24-hours period
- Lower incidence of nocturnal hypoglycemia
- Less weight gain
- Allows for once-daily dosing
- Should not be mixed with other forms of insulin

Insulin Type	Onset	Peak	Duration
Lispro, Aspart	Immediate	15 mins	1-2 hours
Regular	0.5 hour	1-2 hours	4-6 hours
NPH	1-2 hours	4-8 hours	16-20 hours
Insulin glargine	1-2 hours	Peakless	24 hours
Insulin detemir	50-120mins	Relatively flat	Up to 24 hours

Type of insulin

(4) Pre-mixed insulin

Mixtard 30HM (70% Insulin isophane & 30% soluble insulin)

Humulin 70/30 (70% Insulin isophane & 30% insulin neutral)

Novomix 30 (70% protaminated insulin aspart & 30% insulin aspart)

Humalogmix 25 (75% Insulin Lispro Protamine Suspension & 25% Insulin Lispro)

Humalogmix 50 (50% Insulin Lispro Protamine Suspension & 50% Insulin Lispro)

Starting insulin

For Type 2 diabetes

- Start by supplementing the existing OAD regimen with intermediate-acting insulin 0.1-0.2U/Kg/day
- ↑by 2 units at 3-4 daily interval
- If glycemic control fails to improve with 0.5U/Kg/day of insulin or more, a full insulin regimen substituting / replacing the oral regimen is often needed

Starting insulin

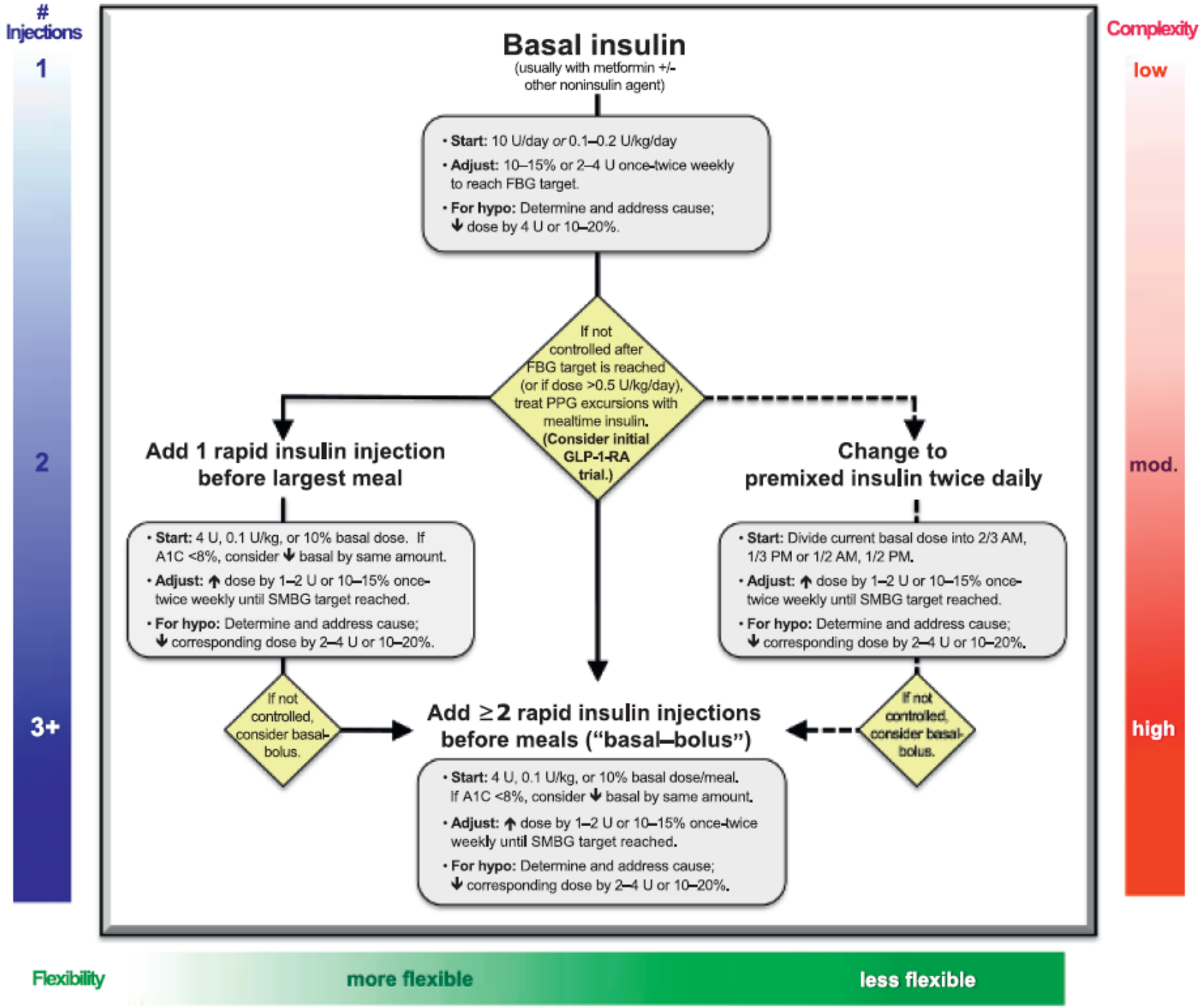
For Type 2 diabetes

- For combination therapy, keep metformin unless contraindicated
- Consider off SU when the total daily insulin dosage is high
- When total daily dose > 40U or pre-dinner hypo. occur, ↓AM dose by 20% and giving as intermediate-acting insulin before dinner

Starting insulin

For Type 2 diabetes

- For replacement of OAD, start with 0.3-0.5U/Kg/day (Usually twice daily NPH)
- If pre-lunch and pre-bedtime ↑BS, treated with mixed regular and intermediate-acting insulin
- In motivated patient, consider change to basal-bolus regimen if glycemic control still poor despite of high daily dose of basal insulin


Injections
1
2
3+
Complexity
low
mod.
high
Basal insulin
(usually with metformin +/- other noninsulin agent)
• Start: 10 U/day or 0.1–0.2 U/kg/day
• Adjust: 10–15% or 2–4 U once-twice weekly to reach FBG target.
• For hypo: Determine and address cause; ↓ dose by 4 U or 10–20%.
If not controlled after FBG target is reached (or if dose >0.5 U/kg/day), treat PPG excursions with mealtime insulin. (Consider initial GLP-1-RA trial.)
Add 1 rapid insulin injection before largest meal
• Start: 4 U, 0.1 U/kg, or 10% basal dose. If A1C <8%, consider ↓ basal by same amount.
• Adjust: ↑ dose by 1–2 U or 10–15% once-twice weekly until SMBG target reached.
• For hypo: Determine and address cause; ↓ corresponding dose by 2–4 U or 10–20%.
If not controlled, consider basal-bolus.
Change to premixed insulin twice daily
• Start: Divide current basal dose into 2/3 AM, 1/3 PM or 1/2 AM, 1/2 PM.
• Adjust: ↑ dose by 1–2 U or 10–15% once-twice weekly until SMBG target reached.
• For hypo: Determine and address cause; ↓ corresponding dose by 2–4 U or 10–20%.
If not controlled, consider basal-bolus.
Add ≥2 rapid insulin injections before meals ("basal–bolus")
• Start: 4 U, 0.1 U/kg, or 10% basal dose/meal. If A1C <8%, consider ↓ basal by same amount.
• Adjust: ↑ dose by 1–2 U or 10–15% once-twice weekly until SMBG target reached.
• For hypo: Determine and address cause; ↓ corresponding dose by 2–4 U or 10–20%.
Flexibility
more flexible
less flexible

Pen-injectors from Novo & Sanofi

NovoNordisk:









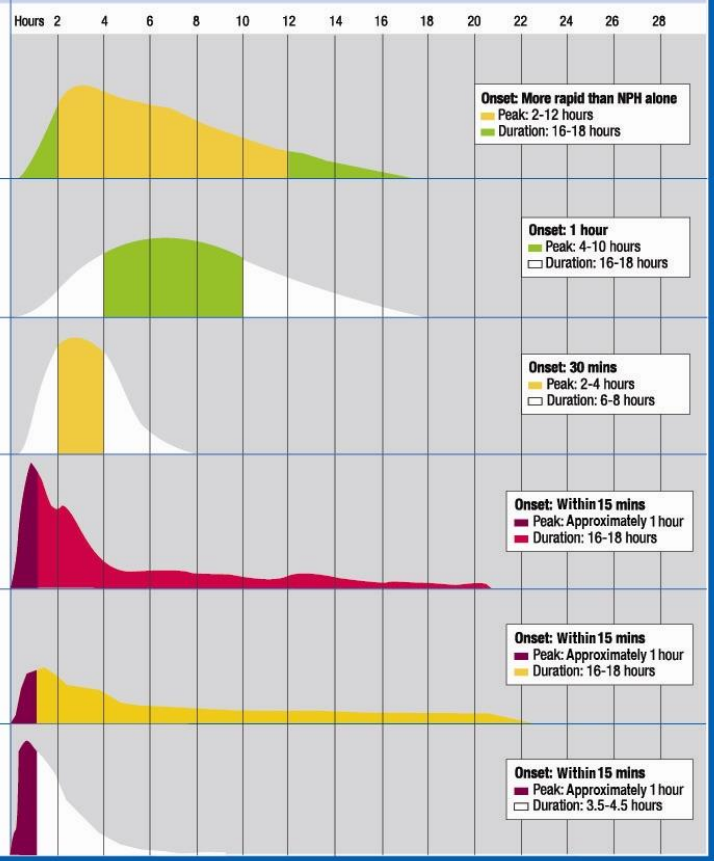
Sanofi-Aventis:



http://www.novonordisk.com/diabetes/public/insulinpens/novopenjunior/benefits.asp.
http://www.diabetologieportal.de/Patienten-und-Interessierte/Injektionshilfen/Weitere-Pens/OptiSet.htm?ID=60
http://www.lantus.com/solostar-insulin-pen/solostar-insulin-pen.aspx. http://www.opticlik.nl/.
http://mein.sanofi-aventis.de/index.php?ID=285&pdb%5Baction%5D=show&pdb%5Bid%5D=702

Different Patients. Different Lifestyles. Different Insulin Needs.

Lilly Brand Name	Type of Insulin (Generic name)	Product Description	Presentation	Schematic Action Profile[1]
Humulin® 70/30 *70% NPH and 30% regular human insulin (recombinant DNA origin)*	70% Insulin Isophane (NPH), 30% Insulin Neutral	PREMIXED INSULIN	**Humulin® 70/30** (Uniformly cloudy or milky) 10 mL vials, and 3 mL cartridges	Onset: More rapid than NPH alone Peak: 2-12 hours Duration: 16-18 hours
Humulin® N *Human insulin isophane (rDNA origin)*	Insulin Isophane (NPH)	INTERMEDIATE ACTING	**Humulin® N** (Uniformly cloudy or milky) 10 mL vials, and 3mL cartridges	Onset: 1 hour Peak: 4-10 hours Duration: 16-18 hours
Humulin® R *Regular human insulin (rDNA origin)*	Insulin Neutral (Soluble)	SHORT-ACTING	**Humulin® R** (Clear and colourless) 10 mL vials, and 3mL cartridges	Onset: 30 mins Peak: 2-4 hours Duration: 6-8 hours
Humalog mix 50™ KwikPen™ 50% insulin lispro (rDNA origin) injection 50% insulin lispro protamine suspension	50% Insulin Lispro, 50% Insulin Lispro Protamine Suspension	PREMIXED INSULIN LISPRO	**Humalog® Mix 50** (Uniformly cloudy or milky) 3 mL cartridges	Onset: Within 15 mins Peak: Approximately 1 hour Duration: 16-18 hours
Humalog mix 25™ KwikPen™ 25% insulin lispro (rDNA origin) injection 75% insulin lispro protamine suspension	25% Insulin Lispro, 75% Insulin Lispro Protamine Suspension	PREMIXED INSULIN LISPRO	**Humalog® Mix 25** (Uniformly cloudy or milky) 3 mL cartridges	Onset: Within 15 mins Peak: Approximately 1 hour Duration: 16-18 hours
Humalog® KwikPen™ insulin lispro (rDNA origin) injection	Insulin Lispro	RAPID-ACTING	**Humalog®** (Clear and colourless) 3 mL cartridges	Onset: Within 15 mins Peak: Approximately 1 hour Duration: 3.5-4.5 hours



Duration of action may vary between patients. ® Eli Lilly registered trademark.

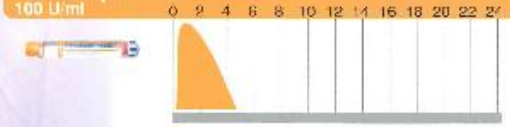
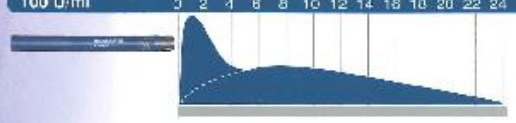
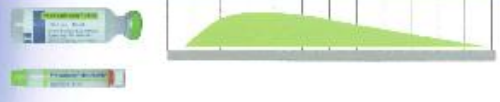
For use by healthcare professionals only.

Before initiating therapy, please refer to full prescribing information.

Eli Lilly Asia, Inc.
Suite 2501-9, 25/F, Tower Two, Times Square, 1 Matheson Street, Causeway Bay, Hong Kong
Tel: (852) 2572 0160 Fax: (852) 2572 7893
www.lilly.com.hk

Novo Nordisk

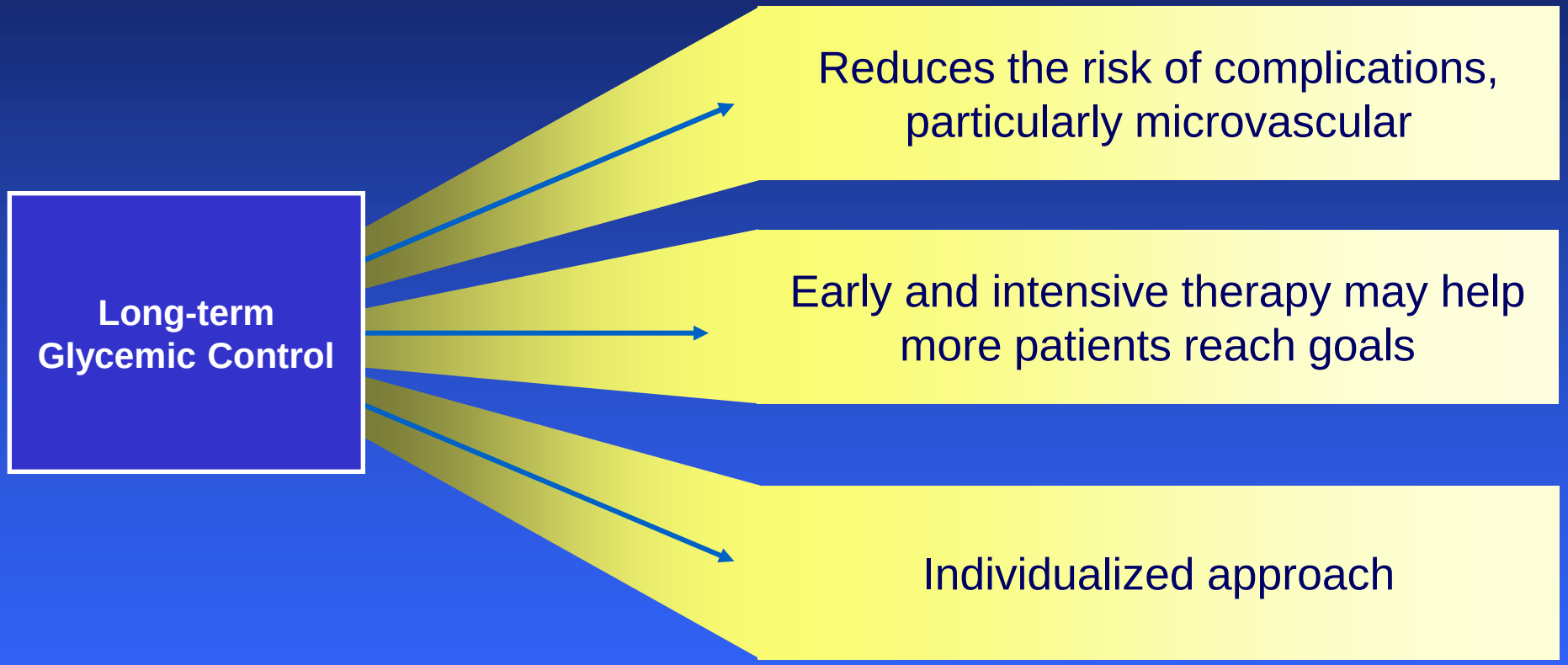
Insulin preparations for every patient in every situation

PREPARATION	APPROXIMATE ONSET OF ACTION, MAXIMUM EFFECT & DURATION	CHARACTERISTICS
NovoRapid® 100 U/ml	 Onset: 10-20 minutes. Maximum effect: 1-3 hours. Duration: 3-5 hours	RAPID-ACTING A clear solution of insulin aspart, with fast onset of action, usually administered three or more daily, should generally be given immediately before the meal or can be given after the meal when necessary.
Levemir® FlexPen® 100 U/ml	 Maximum effect: 3-14 hours. Duration: Up to 24 hours	LONG-ACTING A clear solution of insulin detemir based insulin analogue, usually administered once daily at same time every day, at bedtime or with breakfast.
NovoMix® 30 FlexPen® 100 U/ml	 Onset: 10-20 minutes. Maximum effect: 1-4 hours. Duration: 24 hours	PREMIXED A suspension of premixed insulin analogue consisting 30% insulin aspart and 70% protamine insulin aspart. Administered once, twice or more daily, should generally be given immediately before the meal or can be given after the meal when necessary.
Actrapid® HM 100 IU/ml	 Onset: 0.5 hour. Maximum effect: 1.5-3.5 hours. Duration: 8 hours	SHORT-ACTING A clear solution of human insulin. Administered once or more daily, should be given 30 minutes before the meal.
Protaphane® HM 100 IU/ml	 Onset: 1.5 hours. Maximum effect 4-12 hours. Duration: 24 hours	INTERMEDIATE-ACTING A suspension of human insulin containing protamine (NPH) insulin. Administered once or more daily alone or in combination with Novo Rapid® / Actrapid® HM, or evening before morning with long-acting given at meals.
Mixtard® 30 HM 100 IU/ml	 Onset: 0.5 hour. Maximum effect: 2-8 hours. Duration: 24 hours	PREMIXED A suspension of premixed human insulin containing 30% soluble insulin and 70% isophane (NPH) insulin. Administered once or more daily, should be given 30 minutes before the meal.

Actrapid, Protaphane and other variants may occur depending upon injection site/technique, insulin dosage, diet and exercise.

NB 3 08 09

Bring home message



THANKS