Diabetes
Anterior hypophysis
Diabetes insipidus

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Diabetes

Definition ,classification, type 1 and 2, acute and chronic complications , treatment

Diabetes definition

- Diabetes is a heterogeneous, complex metabolic disorder characterized by elevated blood glucose concentration secondary to either resistance to the action of insulin, insufficient insulin secretion, or both.

Classification of disorders of glycemia

- Type 1- **beta-cell destruction, usually leading to absolute insulin deficiency**
    1. Autoimmune
    2. Idiopathic
- Type 2 – **progressive loss of insulin secretion on background of insulin resistance**
- Other specific types:
    1. Genetic defects of beta-cell function
    2. Genetic defects in insulin action
    3. Diseases of the exocrine pancreas
    4. Endocrinopathies
    5. Drug- or chemical-induced
    6. Infections
    7. Uncommon forms of immune-mediated diabetes
    8. Other genetic syndromes sometimes associated with diabetes
- Gestational diabetes

Criteria for diabetes diagnosis according to ADA 2016

*FPG ≥126 mg/dL (7.0 mmol/L)

Fasting defined as no caloric intake for ≥8 hrs

OR

2-hr PG ≥200 mg/dL (11.1 mmol/L) during OGTT (75-g)*

Using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water

OR

A1C ≥6.5% (48 mmol/mol)*

Perform in lab using NGSP-certified method and standardized to DCCT assay

OR

Random PG ≥200 mg/dL (11.1 mmol/L)

In persons with symptoms of hyperglycemia or hyperglycemic crisis

Factors affecting HbA1C

Increase A1c	Decrease A1c	Various effect on A1c
Age, ethnicity	Hemolytic anemia	Hemoglobinopathy
Splenectomy	Chronic liver disease	CKD
Iron and B12 deficiency	Splenomegaly	
EPO deficiency	Iron, B12 and EPO Tx	
Alcohol, opiates	Antiretroviral drugs, dapsone, ribavirin	

Diabetes type 1

1. Usually caused by autoimmune heterogenic destruction of beta-cells.
2. The prevailing immune process that destructs beta-cells is cellular , mostly T-cell mediated.
3. Pathogenic role of accompanying antibodies is less clear.

Diabetes type 1

1. Roughly 5-15% of all cases of diabetes.
2. Two peaks:5-7 year and adolescence.
3. Yearly incidence of 15-25 cases per 100,000 people younger than 18 years.
4. Finland (60 cases per 100000 people)and Sardinia has the highest prevalence rates for type 1 DM (approximately 20% of the total number of people with DM), while China and Japan have the lowest prevalence rates, with less than 1% of all people with diabetes.

Risk of Type1

Sibling	3.2% (through adolescence); 6% lifetime
Dizygotic twin	6%
Mother	2%
Father	4.6%
Both parents	~10%
Monozygotic twin	50%, but incidence varies with age of index twin

of persons who 95%
develop Type1
DR-3-DQ2
DR4-DR8

Autoantibodies (90% at the diagnosis of type 1)

1. Anti GAD(Glutamic Acid Decarboxilase) 65 .
2. Anti ICA (IA-2) 512.
3. Anti –Insulin.
4. Anti Zn T8.

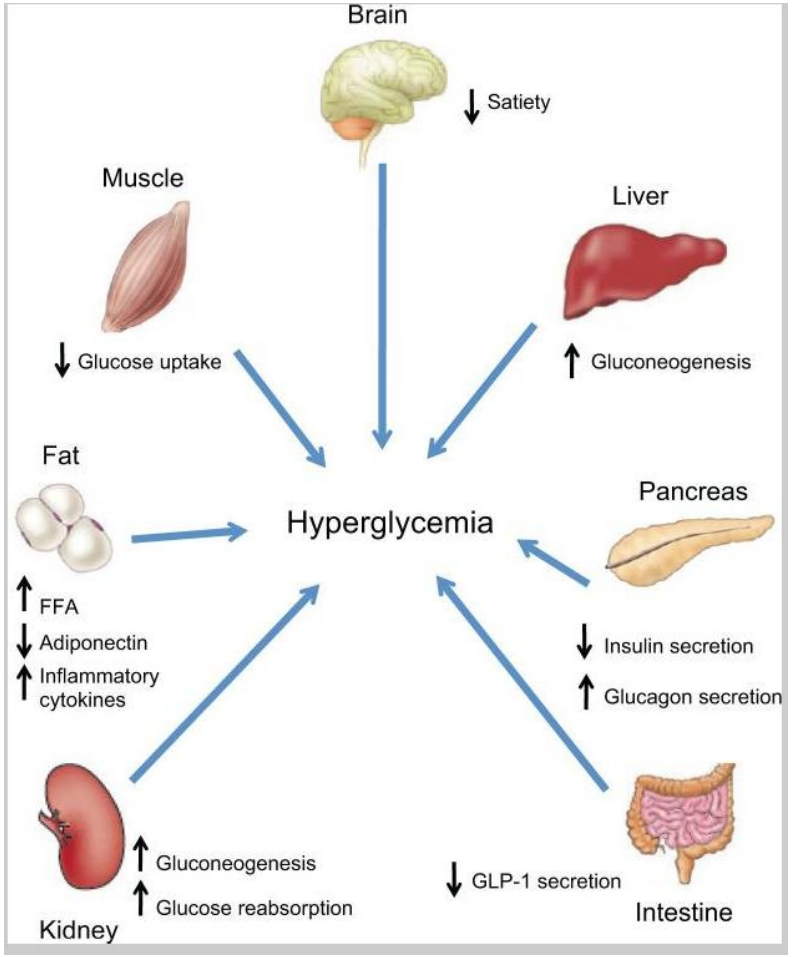
- 4% of normal persons express one of more of the four auto-antibodies.
- Prior probability of disease greatly improved diagnostic value of antibodies .
- Two or more auto-antibodies – risk of 90% for type 1 developement for 10 years.

Characteristic	Type 1 Diabetes	Type 2 Diabetes
Nature *Very different*	Autoimmune disorder marked by destruction of insulin-producing beta cells and loss of insulin production	A disorder of insulin deficiency involving an interplay between both pancreatic and extrapancreatic contributions to disease
Symptoms *Partial overlap*	Rapid onset; very high to extremely high blood glucose levels; polyphagia; polydipsia, polyurea; ketoacidosis	Mild to moderate onset; modest to high elevations in blood glucose; mild polydipsia/polyurea; fatigue; visual changes/headache
Onset *Very different*	Sudden (symptoms for days to weeks)	Slower onset (symptoms for months to years)
Risk factors *Typically different but overlap*	Family history of autoimmune disease but in particular, T1D (10-fold increased risk versus general population)	Overweight/obese; poor diet; sedentary lifestyle; ethnicity (higher in African Americans, Hispanics); family history of T2D; history of gestational diabetes
Onset age *Typically different but overlap*	Typically early life through adolescence but can occur at any age	Typically adults but trending toward earlier age of onset
Treatment strategy *Typically different*	Absolute requirement for insulin (multiple daily injections or insulin pump); self-management lifestyle modification (monitor food types, exercise, etc.)	Dietary modifications and exercise alongside oral agents (for most); increasingly greater percentage of patients require insulin over time
Can it be prevented? *Very different*	Not at present (subject of major research efforts); future cases can be predicted by autoantibodies and genetics	Yes, for over half of potential cases, with dietary modifications and exercise
Can it be reversed? *Very different*	Not at present (subject of major research efforts)	No, but for a limited few; patients can see disease managed and risk for complications reduced through diet modifications, exercise; growing evidence for disease improvements through combination therapies
Complications *Mostly similar, but*	Acute emergencies of hypoglycemia and ketoacidosis leading to hypoglycemic unawareness; chronic effects of hyperglycemia can lead to retinopathy, nephropathy, neuropathy, cardiovascular disease, etc.	Acute emergencies of hypoglycemia and ketoacidosis leading to hypoglycemic unawareness; chronic effects of hyperglycemia can lead to retinopathy, nephropathy, neuropathy, cardiovascular disease, etc.

Diabetes type2

- 90 % of all diabetes in the world
- 9.3% of USA population in 2014(29.1 million people),8.1 million of them was undiagnosed(27.9%)
- 11% of total health spending on adults.
- “Epidemic” of diabetes

Pathogenesis of type 2



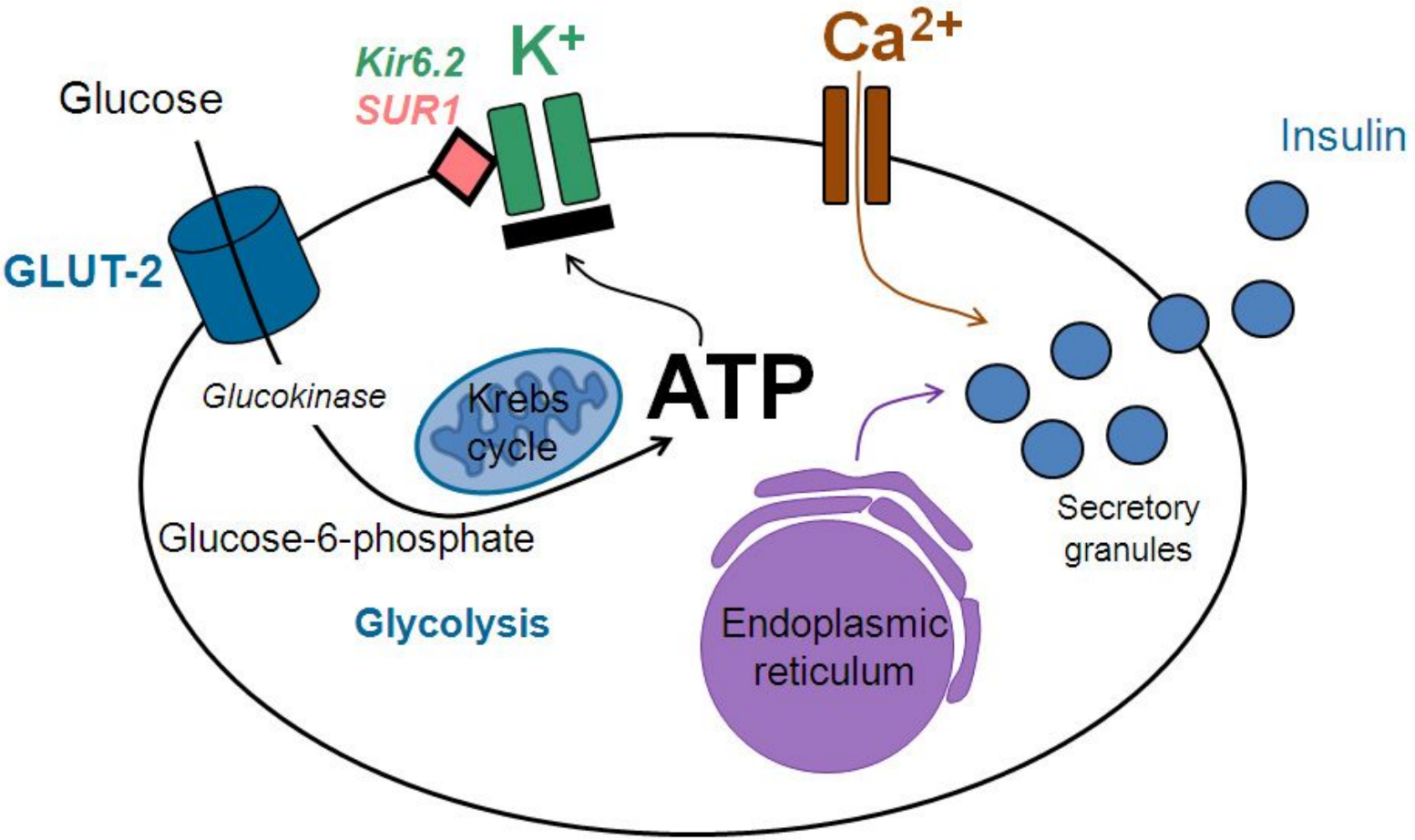
Genetic defects of insulin secretion

- 2-5% of all cases of diabetes mellitus
- Heterogeneous group of diabetes mellitus including MODY **(maturity-onset diabetes of the young)**, mitochondrial diabetes and neonatal diabetes
- Common pathophysiological pathway in monogenic disorders is impaired insulin secretion of the pancreatic beta cell

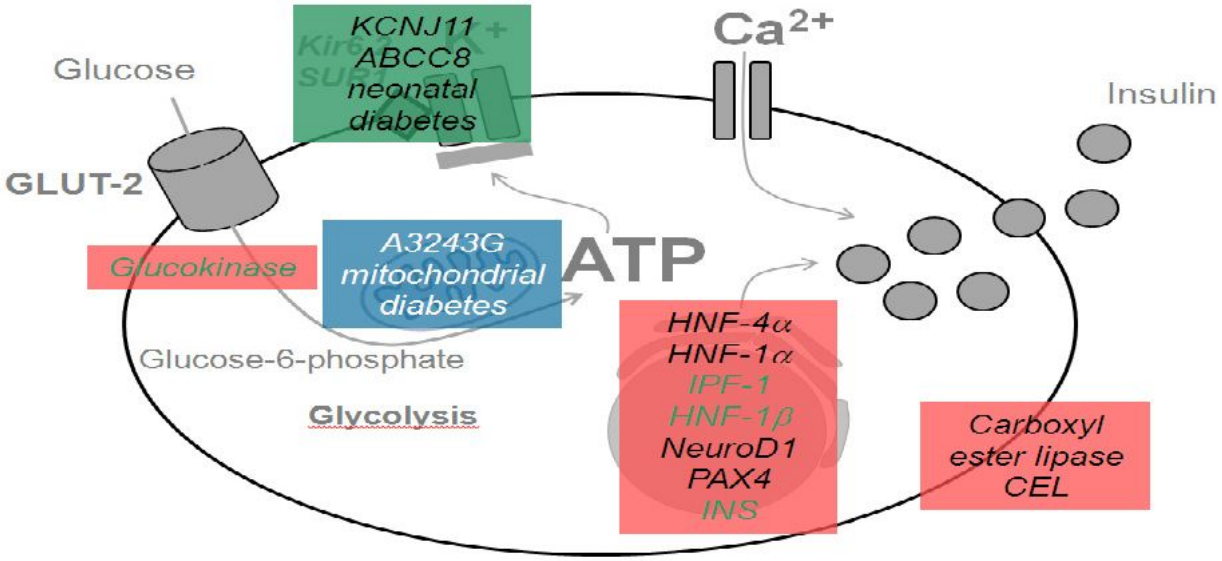
High index of suspicion of MODY

- A family history of diabetes in one parent and first-degree relatives, age at diagnosis usually before 25–30 years.
- Lack of islet autoantibodies (to differentiate from type 1 diabetes at a young age).
- Low or no insulin requirements 2 years after diagnosis.
- Absence of obesity (based on body mass index [BMI] values at diagnosis and follow-up examination).

Beta- cell: insulin secretion



Monogenic defects in insulin secretion



MODY 3(HNF1α mutation)

- Most prevalent MODY:50-70 % of all mutations.
- Onset before age of 30.
- Accented postprandial hyperglycemia (increases over time due to decline of beta cell insulin secretion over time 1-4 % per year).
- Same rate of complication as type 1and 2.
- Very sensitive to sulfonylurea treatment , insulin in pregnancy.

MODY 2

- Mild hyperglycemia started at birth.
- The glucokinase enzyme catalyzes the **rate limiting step** of glucose phosphorylation –”glucose sensor” in the pancreas and liver.
- Mild fasting hyperglycemia.
- No apparent deterioration of beta-cell function.

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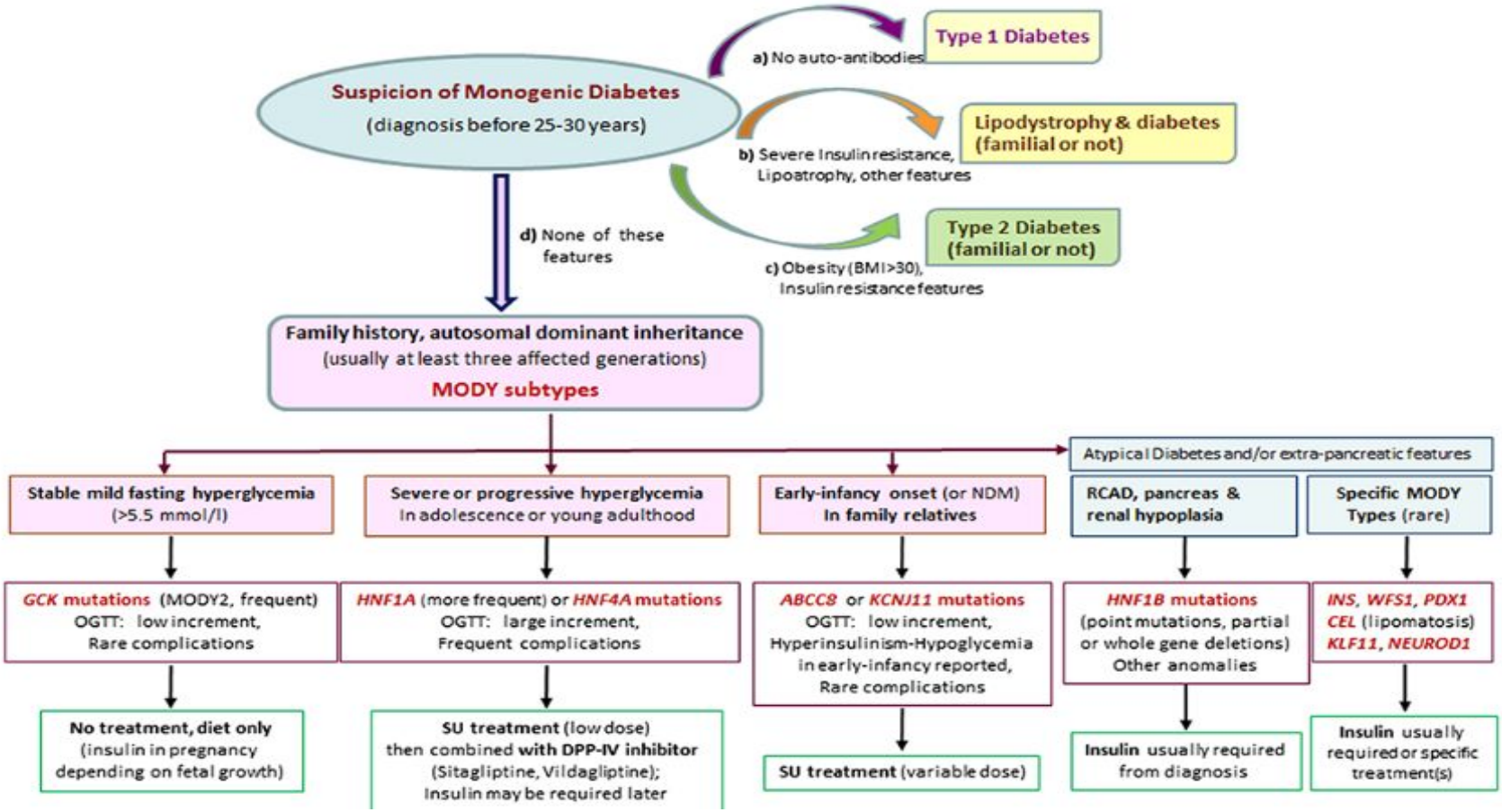
Diagnostic approach to monogenic diabetes



Genetic defects in insulin action

- Rabson Mendenhall :short stature,protuberant abdomen ,teethand nail abnormalities
- **Leprehuanism**: IUGR,fasting hypoglycemia ,death within the first year of life

Mutation of insulin receptor : severe insulin resistance

- Type A insulin resistance: acanthosis nigricans, hyperandrogenism, milder type of resistance than other
- Lipoatrophic diabetes : severe insuline resistance , lipoatrophy ,hypertygliceridemia

Disorder of exocrine pancreas

- Chronic pancreatitis: more than 20 years of disease -80-90% risk of DM.
- Pancreatectomy, pancreatic cancer, CF.
- These form of diabetes are milder than typical DM type 1 because of glucagon deficiency.
- Hemochromatosis.

Endocrinopathies

- Cushing disease and syndrome-glucose intolerance and overt diabetes (30 %).
- Acromegaly –direct anti- insulin effect - from IGT to overt diabetes.
- Pheochromocytoma
- Hyperaldosteronism.
- Somastatinoma and glucagonoma.

examples))Drug and chemicals

- **Ethanol** – chronic pancreatitis-overt diabetes(1% of all diabetes in USA)
- **Glucocorticoids**: inhibition of insulin secretion and insulin resistance.
- Cytotoxic medication(e.g. cyclosporine)-inhibition of insulin release from beta-cell.
- Protease inhibitors-insulin resistance.
- Interferon- β- antibodies to beta cells.
- Pentamidin – beta -cell destruction.
- Vacor –rodentacid- beta- cell destruction.

Infections

- Predisposition to type 1- enteroviruses.
- Direct beta- cells destruction-mumps ,coxsackieviruses B, adenoviruses .
- Congenital rubella ? .
- Abscess and phlegmone of pancreas.

Uncommon immune form of diabetes

- High titers of antibodies to insulin receptors - severe hyperglycemia,acanthosis nigricans
- Hirata syndrome – unusual high titers of auto-insulin antibodies- associated with hypoglycemia.
- Type 1 as a part of different autoimmune syndrome(APS-1,IPEX) or “ mixed type” diabetes in POEMS myeloma.

Pregnancy in women with normal glucose metabolism

- Fasting levels of blood glucose that are lower than in the non-pregnant state due to insulin-independent glucose uptake by the placenta.
- Postprandial hyperglycemia and carbohydrate intolerance as a result of diabetogenic placental hormones.(hPL).

Gestational diabetes mellitus(GDM)

- Disbalance between insulin secretion and increased insulin resistance especially in the third trimester.
- Any degree of glycose intolerance that was recognized during pregnancy.
- The Hyperglycemia and Adverse Pregnancy Outcome **(HAPO)** multinational cohort study a 25,000 pregnant women, demonstrated that risk of adverse maternal, fetal, and neonatal outcomes continuously increased as a function of maternal glycemia at 24–28 weeks.

Screening for GDM

Table 2.5—Screening for and diagnosis of GDM

One-step strategy

Perform a 75-g OGTT, with plasma glucose measurement when patient is fasting and at 1 and 2 h, at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes.

The OGTT should be performed in the morning after an overnight fast of at least 8 h.

The diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded:

- Fasting: 92 mg/dL (5.1 mmol/L)
- 1 h: 180 mg/dL (10.0 mmol/L)
- 2 h: 153 mg/dL (8.5 mmol/L)

Two-step strategy

Step 1: Perform a 50-g GLT (nonfasting), with plasma glucose measurement at 1 h, at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes.

If the plasma glucose level measured 1 h after the load is ≥140 mg/dL* (7.8 mmol/L), proceed to a 100-g OGTT.

Step 2: The 100-g OGTT should be performed when the patient is fasting.

The diagnosis of GDM is made if at least two of the following four plasma glucose levels (measured fasting and 1 h, 2 h, 3 h after the OGTT) are met or exceeded:

	Carpenter/Coustan (55)	or	NDDG (56)
• Fasting	95 mg/dL (5.3 mmol/L)		105 mg/dL (5.8 mmol/L)
• 1 h	180 mg/dL (10.0 mmol/L)		190 mg/dL (10.6 mmol/L)
• 2 h	155 mg/dL (8.6 mmol/L)		165 mg/dL (9.2 mmol/L)
• 3 h	140 mg/dL (7.8 mmol/L)		145 mg/dL (8.0 mmol/L)

Algorithm of glucose testing in pregnancy

- All women have to be screened for diabetes as essential part of pregnancy planning and be counseled about importance of strict glycemic control in pregnancy.
- All women must be tested for diabetes in the first pregnancy visit (as early as possible in the first trimester).
- 6-12 week after delivery all women with GDM have to undergo **OGTT with 75 gram glucose load** in order to rule out or rule in persistent diabetes or prediabetes(IGT).
- Treatment of woman with previous GDM and IGT with lifestyle intervention and metformin can delay or prevent diabetes in the future(30-40% for 10 years comparing with placebo , for 3 years NNT is 5-6 for 1 case) .

Goals of diabetes treatment

- Prevent macrovasular diabetes complication-cardiovascular disease (IHD, diabetic cardiomyopathy, TIA, fatal and non- fatal CVA).
- Prevent microvascular diabetes complication:

1. Retinopathy
2. Neuropathy
3. Nephropathy- diabetic kidney disease

- Alleviate hyperglycemic symptoms.
- Prevent/treat diabetic ketoacidosis(DKA) and non-ketotic hyperosmolar state (coma).

Aspects of diabetes treatment

- Glycemic control
- Lifestyle intervention include obesity treatment
- Medical nutritional therapy
- Control of high blood pressure
- Control of dyslipidemia
- Anti-agreggant therapy

Glycemic control and diabetic complication

- Type 1 study:
  DCCT –EDIC(Diabetes Control and Complication Trial-Epidemiology of Diabetes Control and Complications)
- Principal type 2 studies:

1. UKPDS(The UK Prospective Diabetes Study).
2. ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation).
3. ACCORD (Action to Control Cardiovascular Risk in Diabetes).
4. VADT(Veteran Affairs Diabetes Trial).

- Be careful of new “wonder” drugs for diabetes and “smashing hit” studies!!!

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THE EFFECT OF INTENSIVE TREATMENT OF DIABETES ON THE DEVELOPMENT AND PROGRESSION OF LONG-TERM COMPLICATIONS IN INSULIN-DEPENDENT DIABETES MELLITUS

THE DIABETES CONTROL AND COMPLICATIONS TRIAL RESEARCH GROUP*

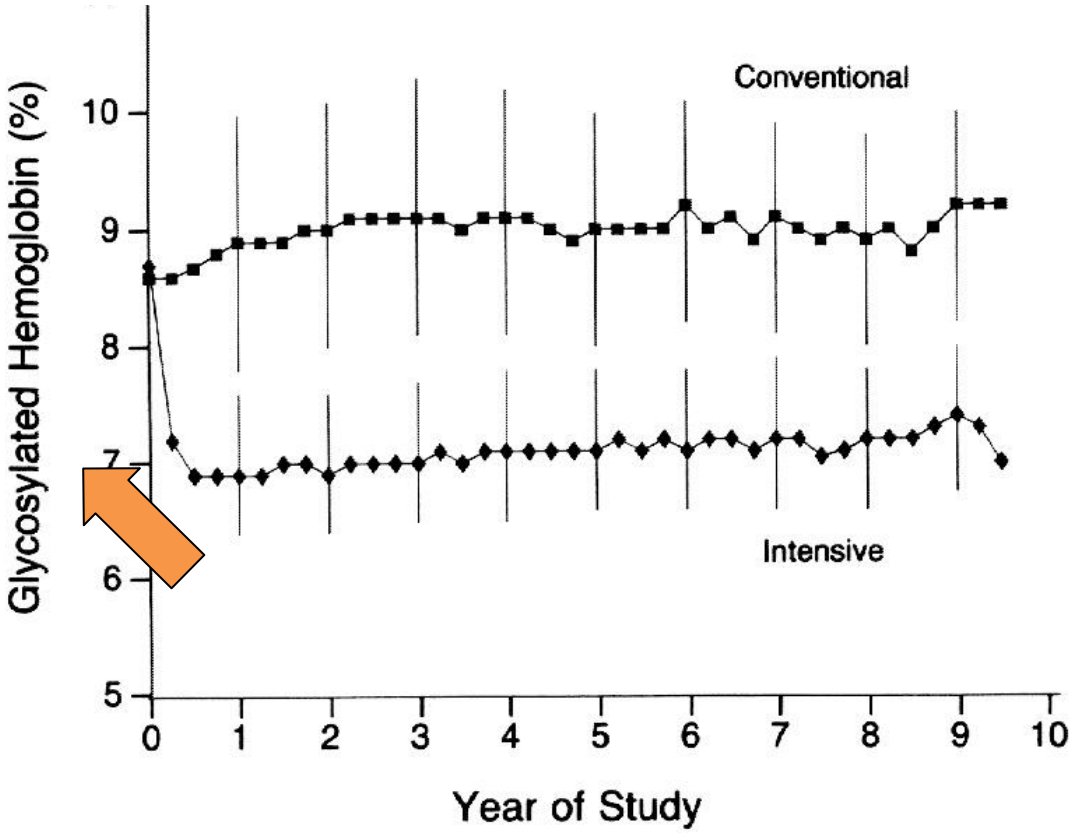
DCCT

N = 1441 T1DM

Intensive
(≥ 3 injections/day or CSII)

vs.

Conventional
(1-2 injections per day)



Inclusion criteria for DCCT

- **Primary prevention group** : DM type 1: 1-5 years, no retinopathy or severe diabetic complication, no hypertension or hypercholesteremia, no severe medical condition: urinary microalbumin less than 40 mg for 24 hour .
- **Primary intervention group**: the same duration of diabetes, very mild –to moderate non-prolipherative retinopathy, albumin secretion less than 400 mg for 24 hours, no severe diabetic complication ,no hypertension or hypercholesteremia, no severe medical condition.

Baseline characteristics

Table 1. Base-Line Characteristics of the Two Study Cohorts.*

Characteristic	Primary Prevention		Secondary Intervention	
	Conventional therapy (N = 378)	Intensive therapy (N = 348)	Conventional therapy (N = 352)	Intensive therapy (N = 363)
Age (yr)	26±8	27±7	27±7	27±7
Adolescents, 13–18 yr (%)	19	16	9	10
Male sex (%)	54	49	54	53
White race (%)	96	96	97	97
Duration of IDDM (yr)	2.6±1.4	2.6±1.4	8.6±3.7	8.9±3.8
Insulin dose (U/kg of body weight/day)	0.62±0.26	0.62±0.25	0.71±0.24	0.72±0.23
Glycosylated hemoglobin (%)†	8.8±1.7	8.8±1.6	8.9±1.5	9.0±1.5

Goals and modes of therapy conventional group

- **Conventional group therapy goals**: to prevent symptoms attributable to glycemia or glycosuria, absence of ketones in urine, maintenance of normal growth development ," ideal " body weight ,freedom from severe and frequent hypoglycemia.
- **Treatment of conventional group** :one or two insulin injection including mixed intermediate and rapid acting insulin, self -monitoring of blood and urine glucose, education about diet and exercise, no usual daily adjustment of insulin dose .

Goals and modes of treatment intensive treatment group

- 3 or more insulin injection or pump therapy.
- Self monitoring of blood glucose at least 4 times a day.
- Dose or method adjustment to treatment goals :

1. fasting glucose 70-120 mg/dl
2. postprandial of less than 180 mg/dl
3. Weekly 3a.m. more than 65 mg/dl
4. HbA1- 6 % and less

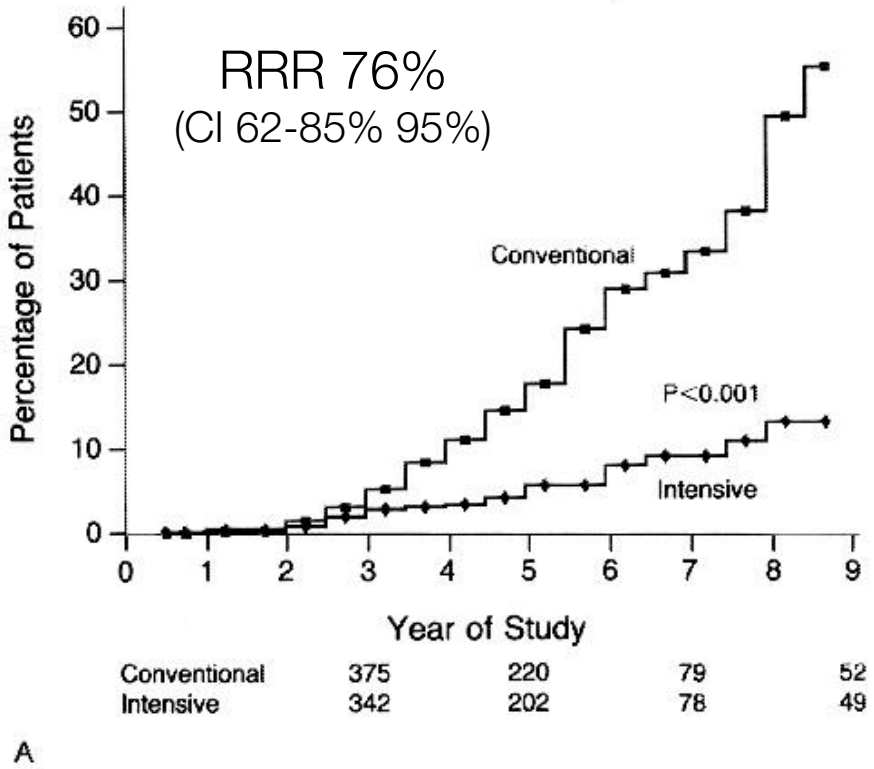
- Women who were planning a pregnancy or became pregnant receive intensive therapy until the time of delivery .

Study questions

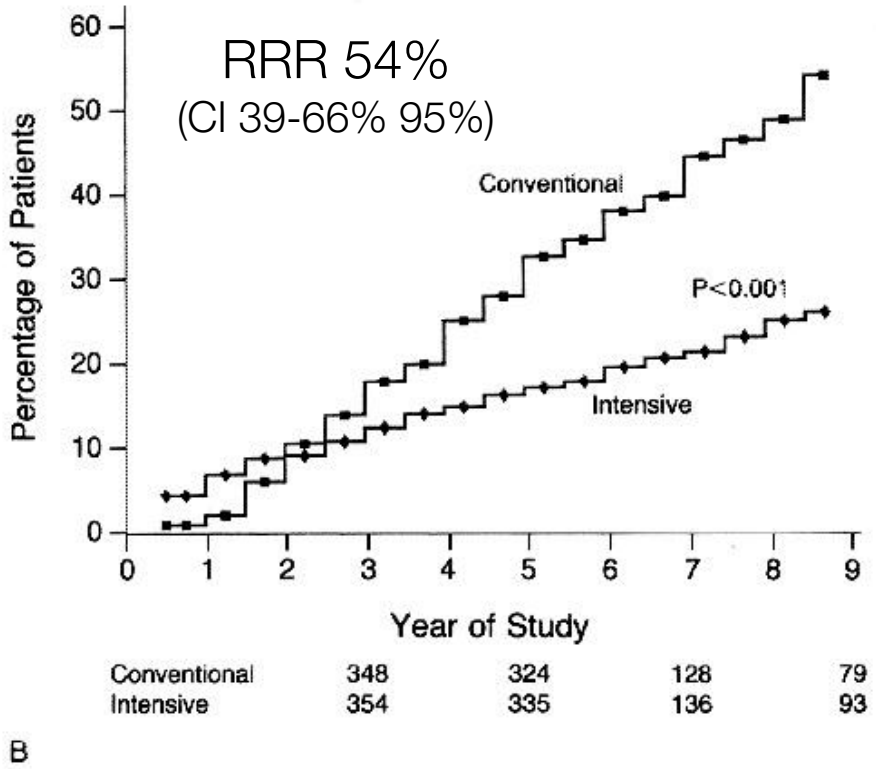
- Prevention of diabetic retinopathy in primary prevention group by intensive treatment versus conventional group .
- Influence on progression of diabetic retinopathy in secondary intervention groupintensive treatment versus conventional group .
- Renal, neurologic, neuropsychological cardiovascular outcomes in two groups.
- Adverse effect of two modes of treatment.

Reduction in Retinopathy

Primary Prevention



Secondary Intervention

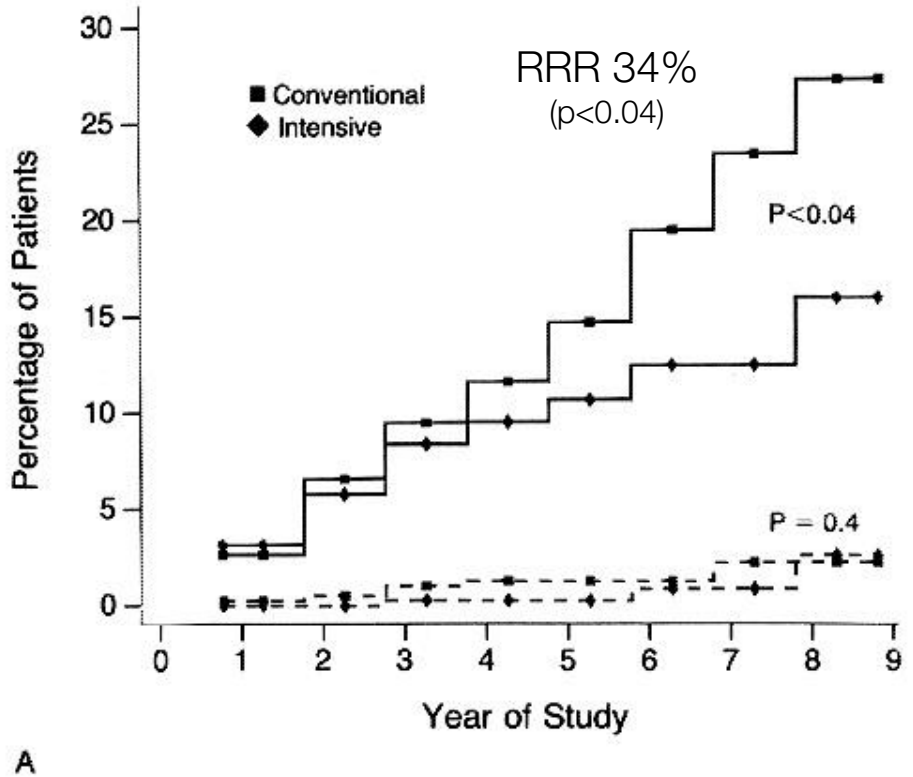


RRR = relative risk reduction CI = confidence interval

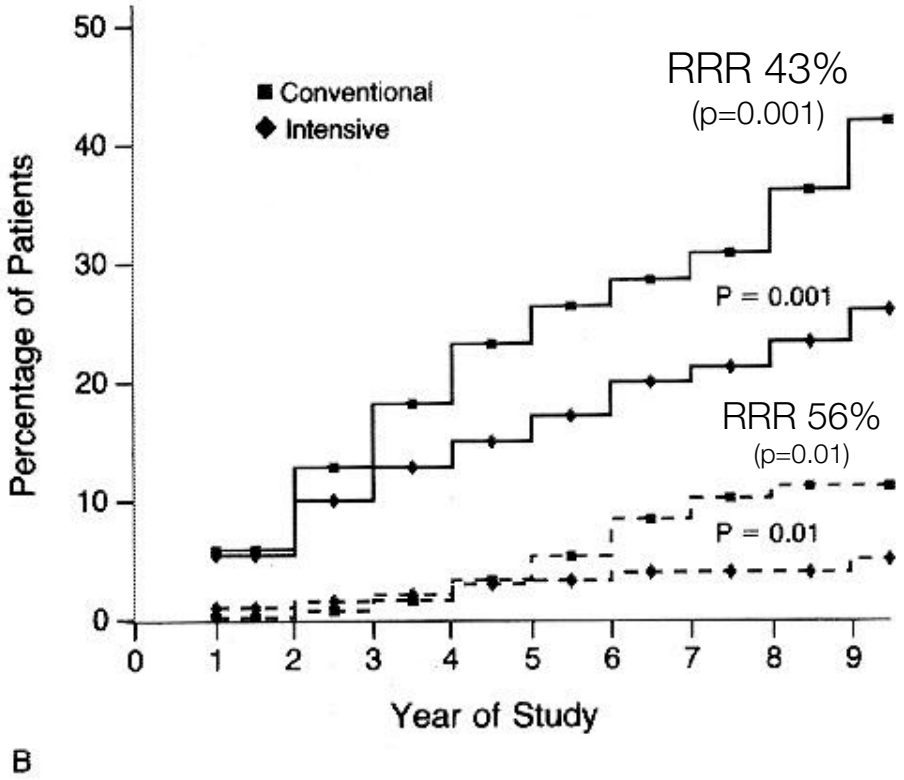
.The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993;329:977-986

DCCT: Reduction in Albuminuria

Primary Prevention



Secondary Intervention

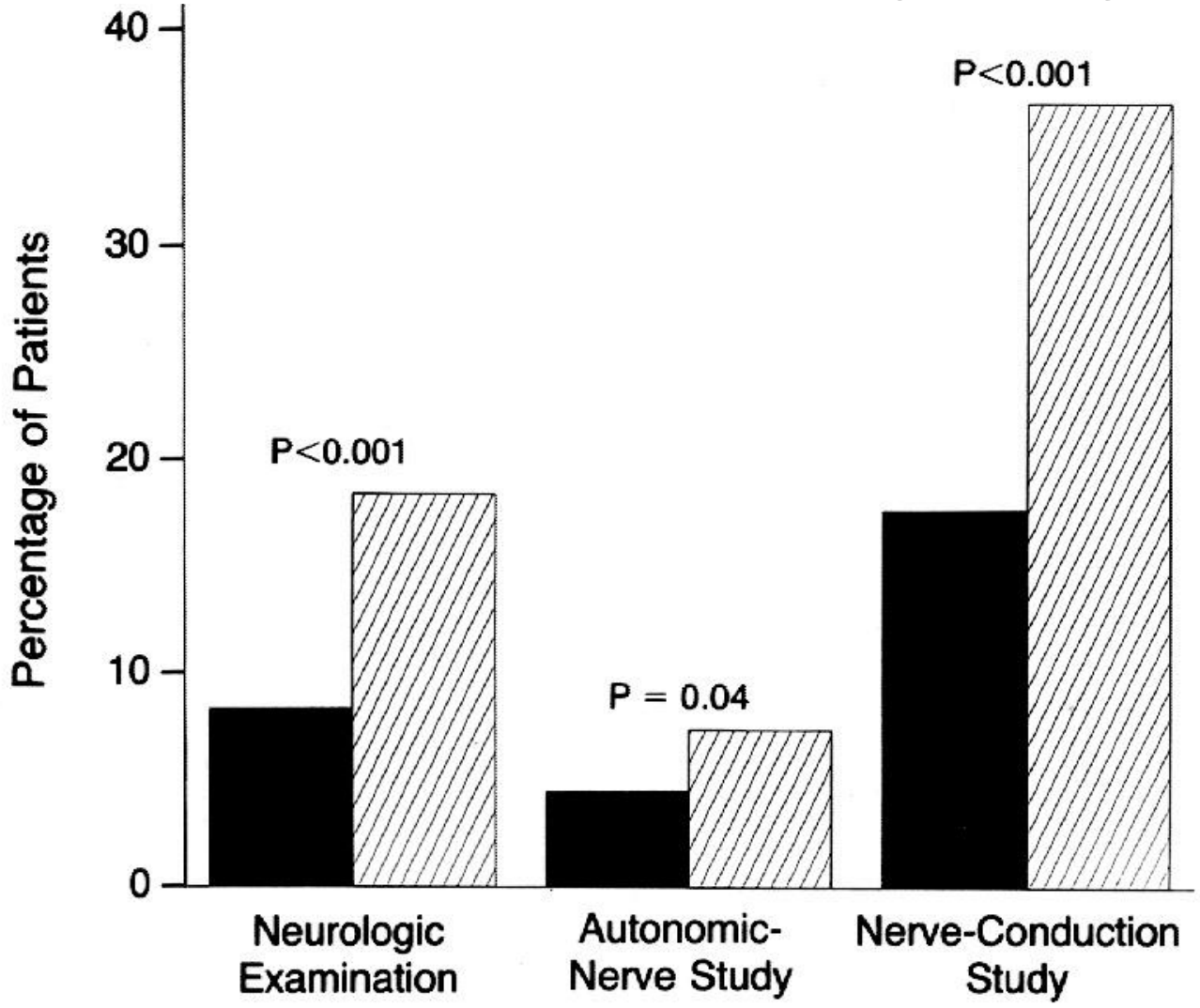


Solid line = risk of developing microal
Dashed line = risk of developing macroal

RRR = relative risk reduction
CI = confidence interval

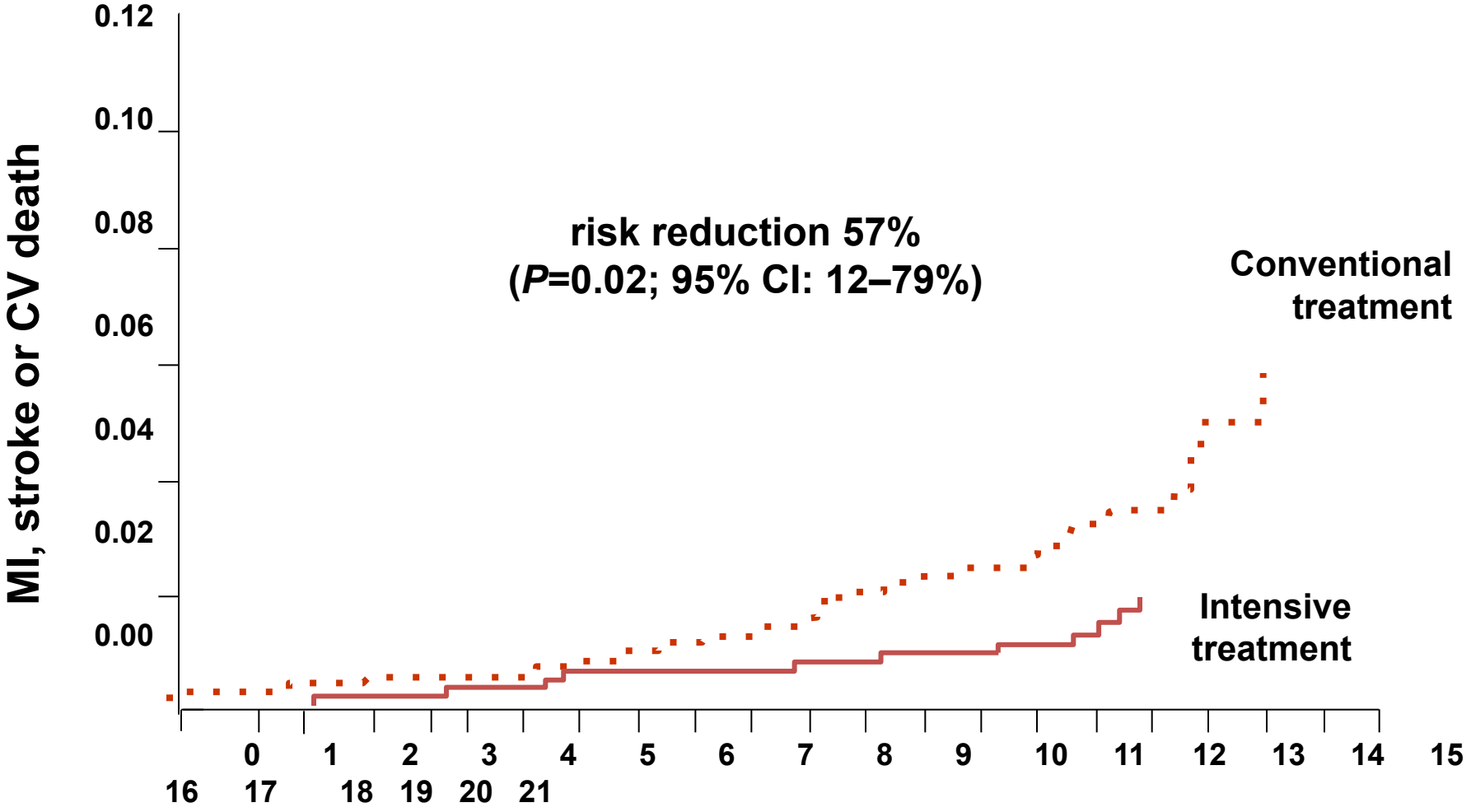
.The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993;329:977-986

Reduction in Neuropathy



.The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993;329:977-986

Reduction of cardiovascular event in DCCT –EDIC



.DCCT/EDIC Study Research Group. *N Engl J Med* 2005;353:2643–2653

Hypoglycemia and other adverse events

- General and severe hypoglycemia 3 times higher in intensively treatment group including coma and seizures.
- Weight gain 4.6 kg more in intensively treated group.
- No death , no more cardiovascular events during hypoglycemia.
- No decline of quality of life, no difference in neuropsychological functioning.
- May be more MVA in cases of severe hypoglycemia.

GLYCEMIC CONTROL IN TYPE 2 UKPDS

- 20-year interventional trial from 1977 to 1997.
- **5,102** patients with newly-diagnosed type 2 diabetes recruited between 1977 and 1991.
- Median follow-up 10.0 years, range 6 to 20 years.

UKPDS: Aims

- To determine **whether improved glucose control of Type 2 diabetes will prevent clinical complications**

- Does therapy with
  - **sulphonylurea** - first or second generation
  - **insulin**
  - **metformin**

  has any specific advantage or disadvantage

UKPDS patient characteristics

5102 newly diagnosed Type 2 diabetic patients

age 25 - 65 y *mean* **53 y**

gender male : female 59 : 41%

ethnic group Caucasian 82% Asian 10%

BMI *mean* **28 kg/m^2**

FPG ***median*** **11.5 mmol/L (207 mg/dl)**

HbA_{1c} ***median*** **9.1 %**

hypertensive **39%**

Treatment Policies in 3867 patients

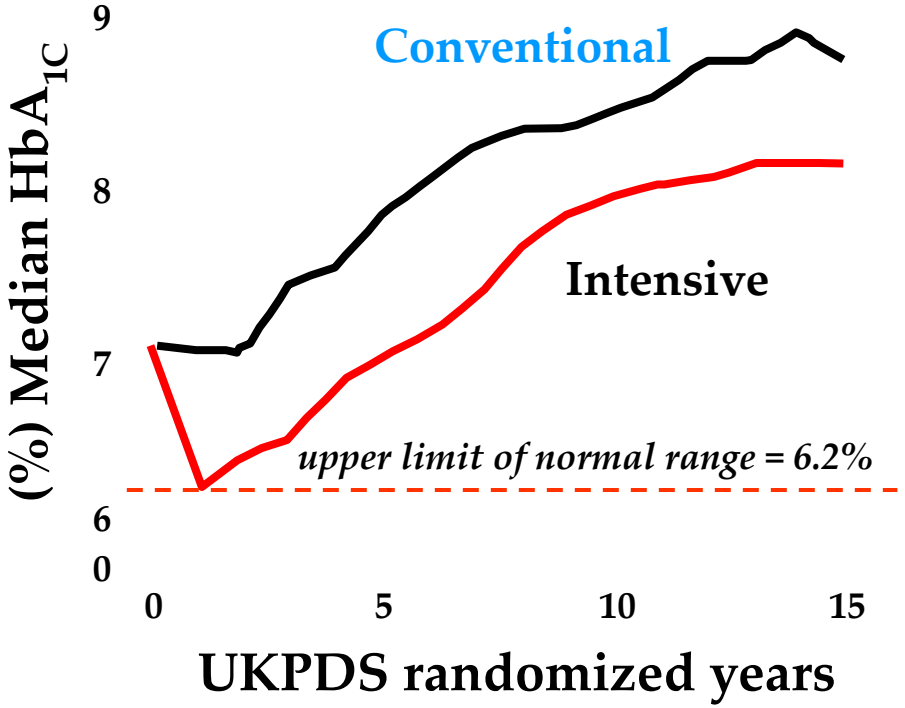
Conventional Policy n = 1138

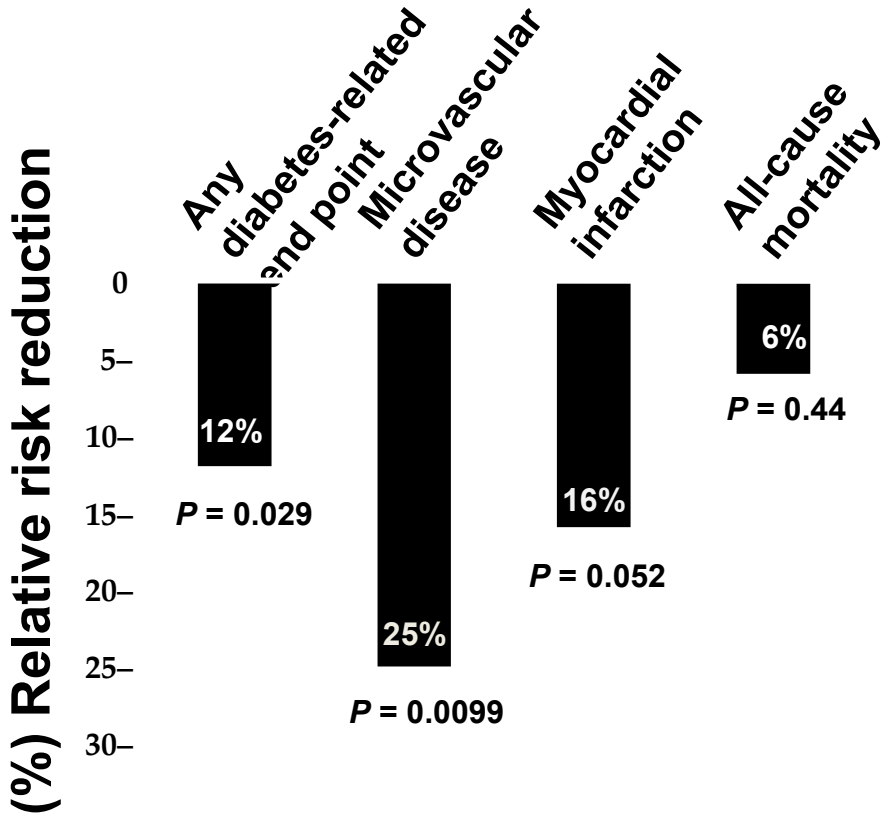
- initially with diet alone
- aim for near normal weight, best fasting plasma **glucose < 15 mmol/l (270 mg/dl)**, asymptomatic
- when marked hyperglycaemia develops
  allocate to non-intensive pharmacological therapy

Intensive Policy with sulphonylurea or insulin n = 2729

- aim for fasting plasma glucose < **6 mmol/L(108 mg/dl),** asymptomatic
- when marked hyperglycaemia develops
  on sulphonylurea add metformin, move to insulin therapy
  on insulin, transfer to complex regimens

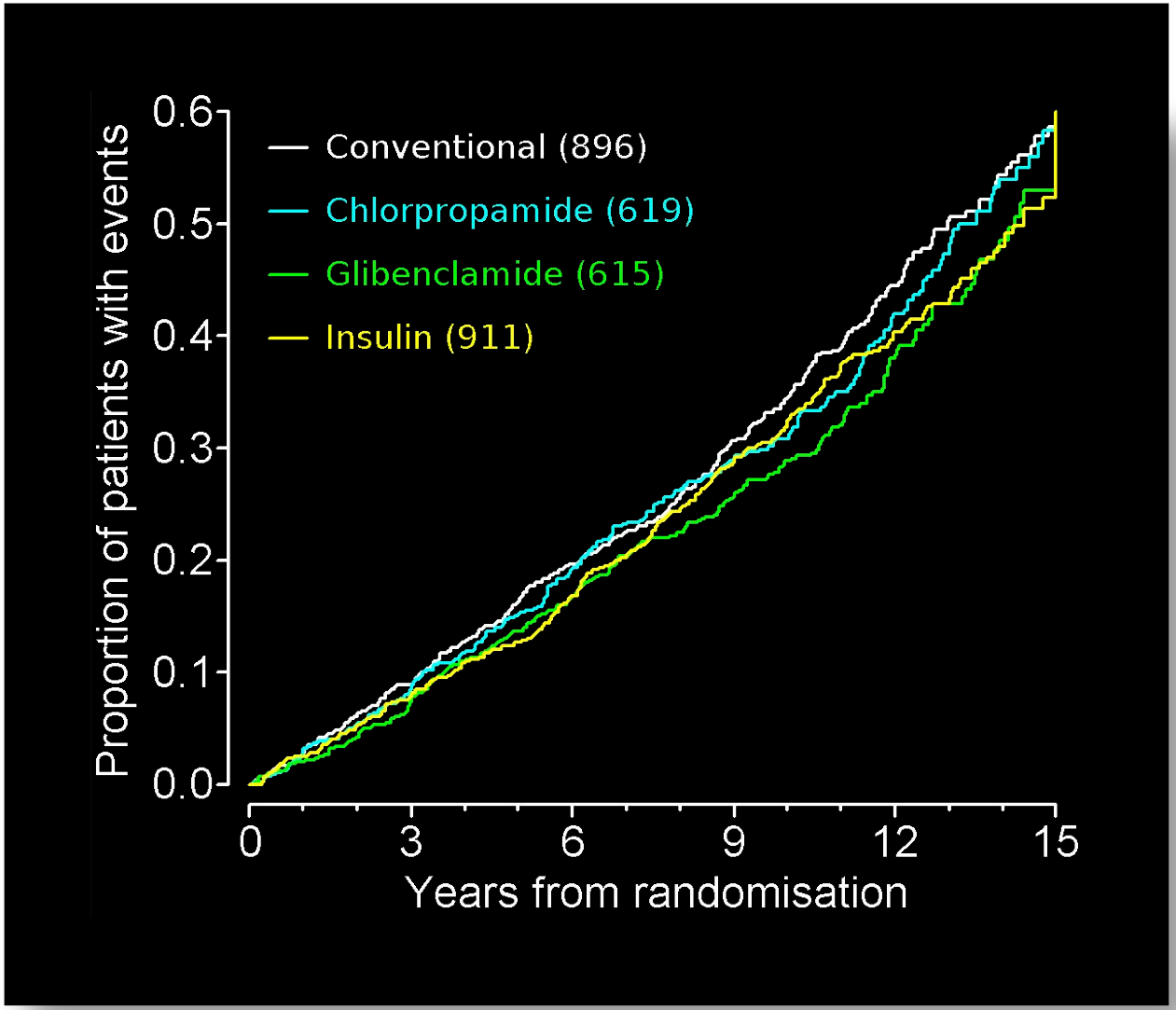
UKPDS: intensive control reduces complications in type 2 diabetes



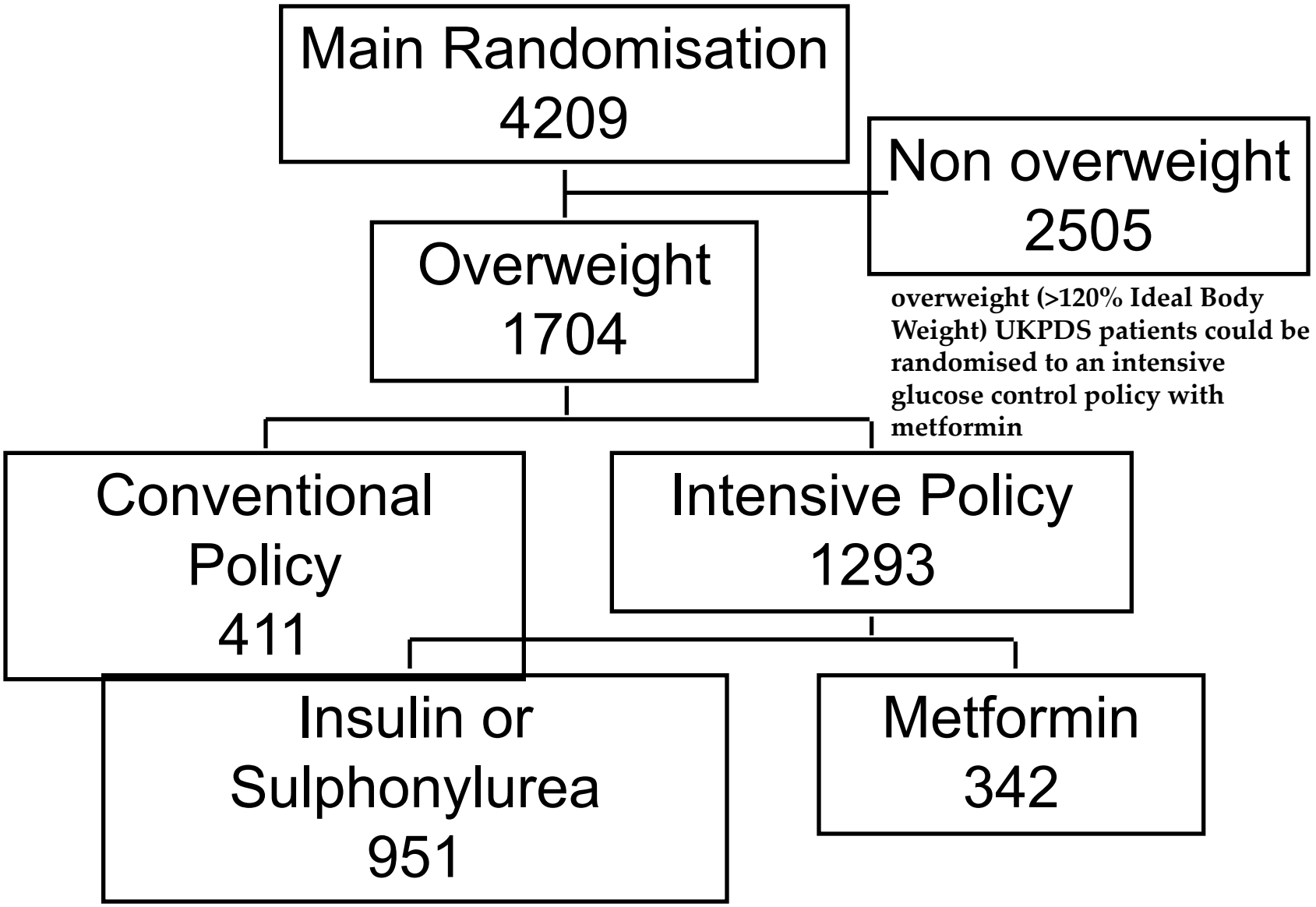


UKPDS Study Group. *Lancet* 1998; **352:**837–853.

UKPDS
Any diabetes related endpoints



UKPDS- metformin



Metformin in overweight patients in comparison with conventional treatment

- 32% risk reduction in any diabetes-related endpoints, p=0.0023
- 42% risk reduction in diabetes-related deaths, p=0.017
- 36% risk reduction in all cause mortality, p=0.011
- 39% risk reduction in myocardial infarction,p=0.01

ACCORD trial

- **10251** patients with diabetes with HbA1c 7.6-8.9 randomly assigned to intensive therapy in order to achieve HbA1c below 6% versus standard therapy (HbA1c 7-7.5%).
- **4733** patients were randomly assigned to lower their blood pressure by receiving either intensive therapy (systolic blood-pressure target, <120 mm Hg) or standard therapy (systolic blood-pressure target, <140 mm Hg).
- **5518** patients were randomly assigned to receive either fenofibrate or placebo while maintaining good control of low-density lipoprotein cholesterol with simvastatin.
- **Mean age 62 years ,10 years of diagnosed diabetes, with 35% CVD in baseline.**

Treatment group

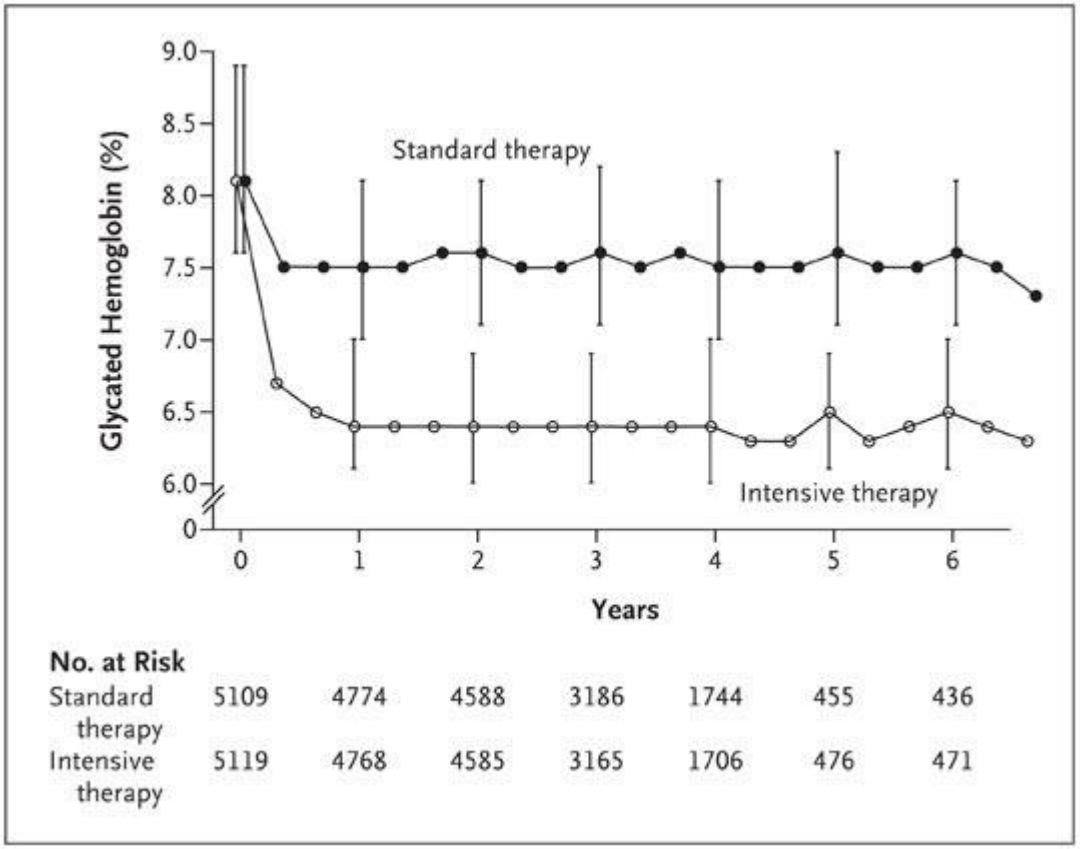
VBWG

ACCORD: Glucose-lowering drugs by treatment strategy

	Patients (%)	
	Intensive therapy (n = 5128)	Standard therapy (n = 5123)
Metformin	94.7	86.9
Secretagogue	86.6	73.8
Thiazolidinedione	91.7	58.3
α-Glucosidase inhibitor	23.2	5.1
Incretin	17.8	4.9
Insulin	77.3	55.4

ACCORD Study Group. *N Engl J Med.* 2008;358:2545-59.

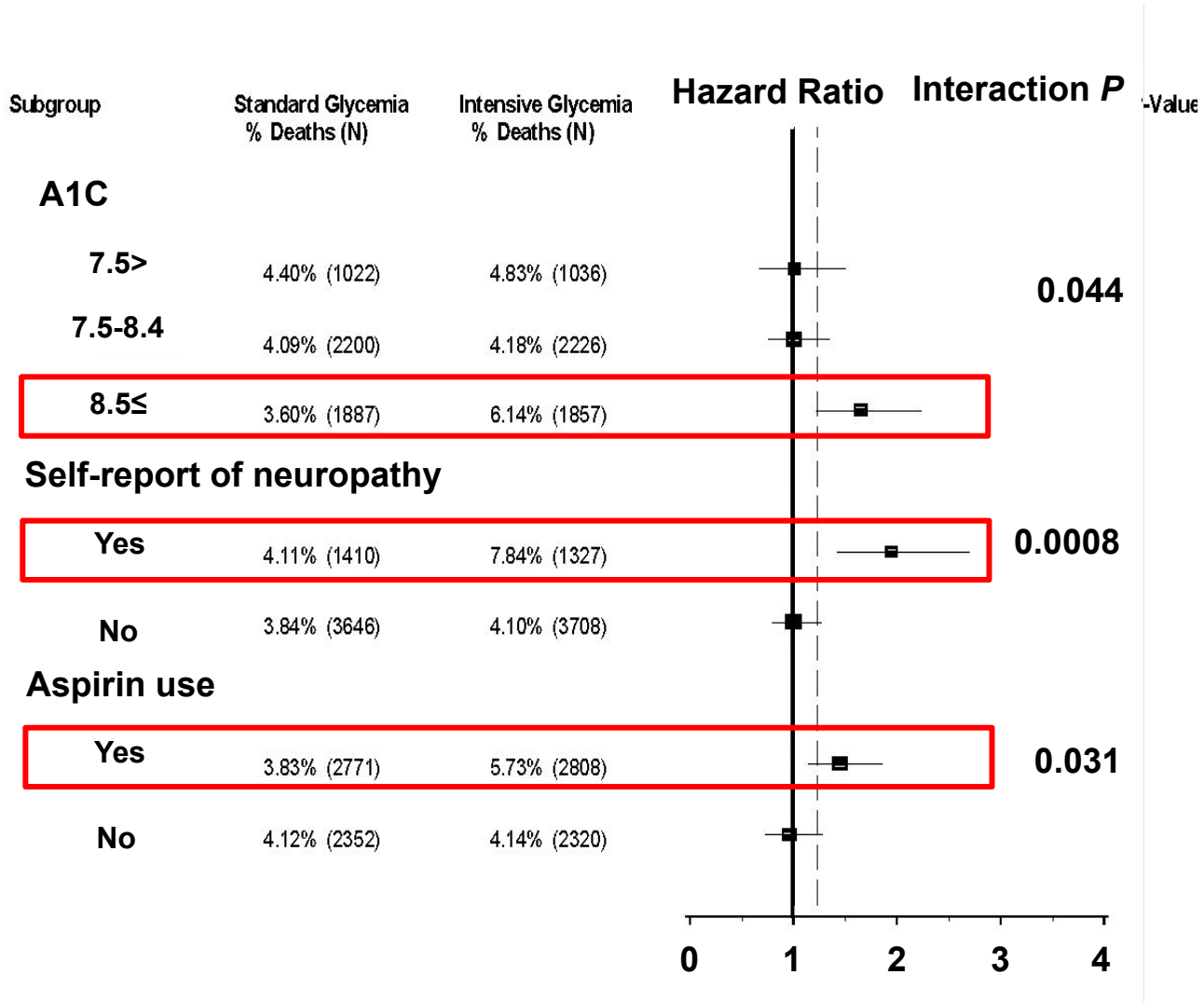
ACCORD study (glycemic arm)



Results of the Randomized Comparison of an Intensive Versus a Standard Glycemic Strategy

	Unadjusted HR for Intensive vs. Standard (95% CI)	*P*-value
All-cause mortality	1.22 (1.01-1.46)	0.04
Primary endpoint: CV death, MI, stroke	0.90 (0.78-1.04)	0.16
CV death	1.35 (1.04-1.76)	0.02
Non-fatal MI	0.76 (0.62-0.92)	0.004
Non-fatal stroke	1.06 (0.75-1.50)	0.74

ACCORD study glycemic group



ADVANCE collaborative group

Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes

The ADVANCE Collaborative Group*

ABSTRACT

BACKGROUND

In patients with type 2 diabetes, the effects of intensive glucose control on vascular outcomes remain uncertain.

METHODS

We randomly assigned 11,140 patients with type 2 diabetes to undergo either standard glucose control or intensive glucose control, defined as the use of gliclazide (modified release) plus other drugs as required to achieve a glycated hemoglobin value of 6.5% or less. Primary end points were composites of major macrovascular events (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) and major microvascular events (new or worsening nephropathy or retinopathy), assessed both jointly and separately.

Results of intensive glucose lowering in ADVANCE trial

- Average lowering of HbA1c from 7.2 to 6.5%
- Similar base line characteristic of patients. (**average age :66 years**, **diabetes duration of 8 years in average , prevalence of CVD 32%)**

Intensive glucose lowering (to a mean HbA1c of 6.5%) in patients with type 2 DM resulted in:

- 10% reduction in the combined primary macrovascular or microvascular outcome (p=0.01)
- 14% reduction in microvascular events (p=0.01)
- 21% reduction in new or worsening nephropathy (p<0.01)
- 65% reduction in end stage kidney disease (p=0.02)
- No reduction (or excess) mortality

VA Diabetes Trial (VADT)

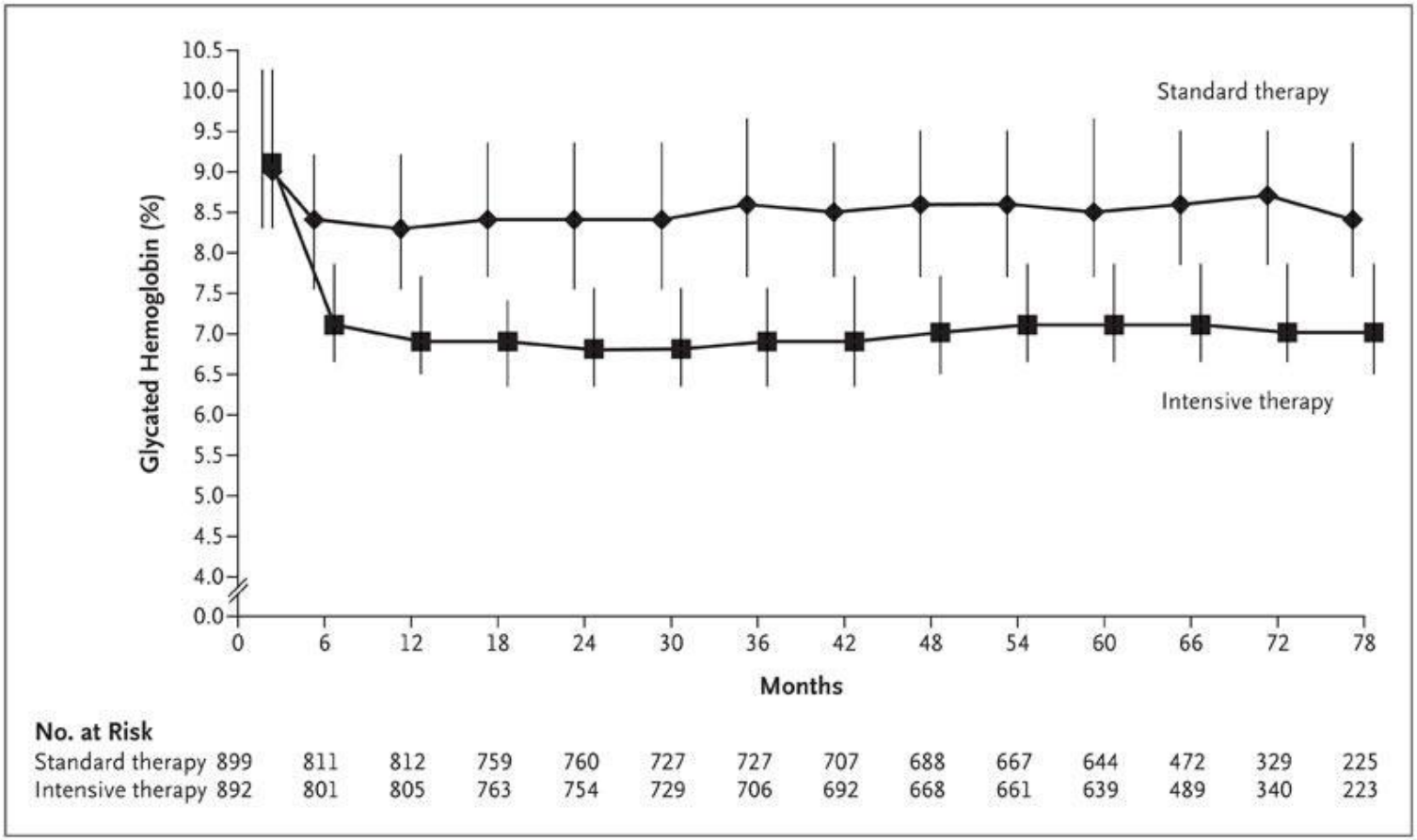
- Similar study design: intensive therapy versus standard therapy.
- Primary endpoint: first CVD event after randomization.
- Subjects with longer durations of diabetes, more CVD, higher baseline A1C.

Differences in ACCORD/ADVANCE/VADT

BASELINE	ACCORD	ADVANCE	VADT
No of patients	10,251	11,140	1,791
Diabetes duration (years)	10	8	11.5
Hist. macrovasc. dis. (%)	35	32	40
Baseline A1C (%)	8.1	7.2	9.4
Intervention			
Target A1C (%)	<6	≤6.5	<6.5
Insulin Rx (%)	77 vs. 55	40 vs. 24	89 vs. 74
TZD Rx (%)	92 vs. 58	17 vs. 11	53 vs. 42
Outcome (intensive vs. standard)			
Median A1C @ study end	6.4 vs. 7.5%	6.4 vs. 7.0%	6.9 vs. 8.5%
Death: any cause	5.0 vs. 4.0%*	8.9 vs. 9.6%	3.7 vs. 4.5%

*$P < 0.05$

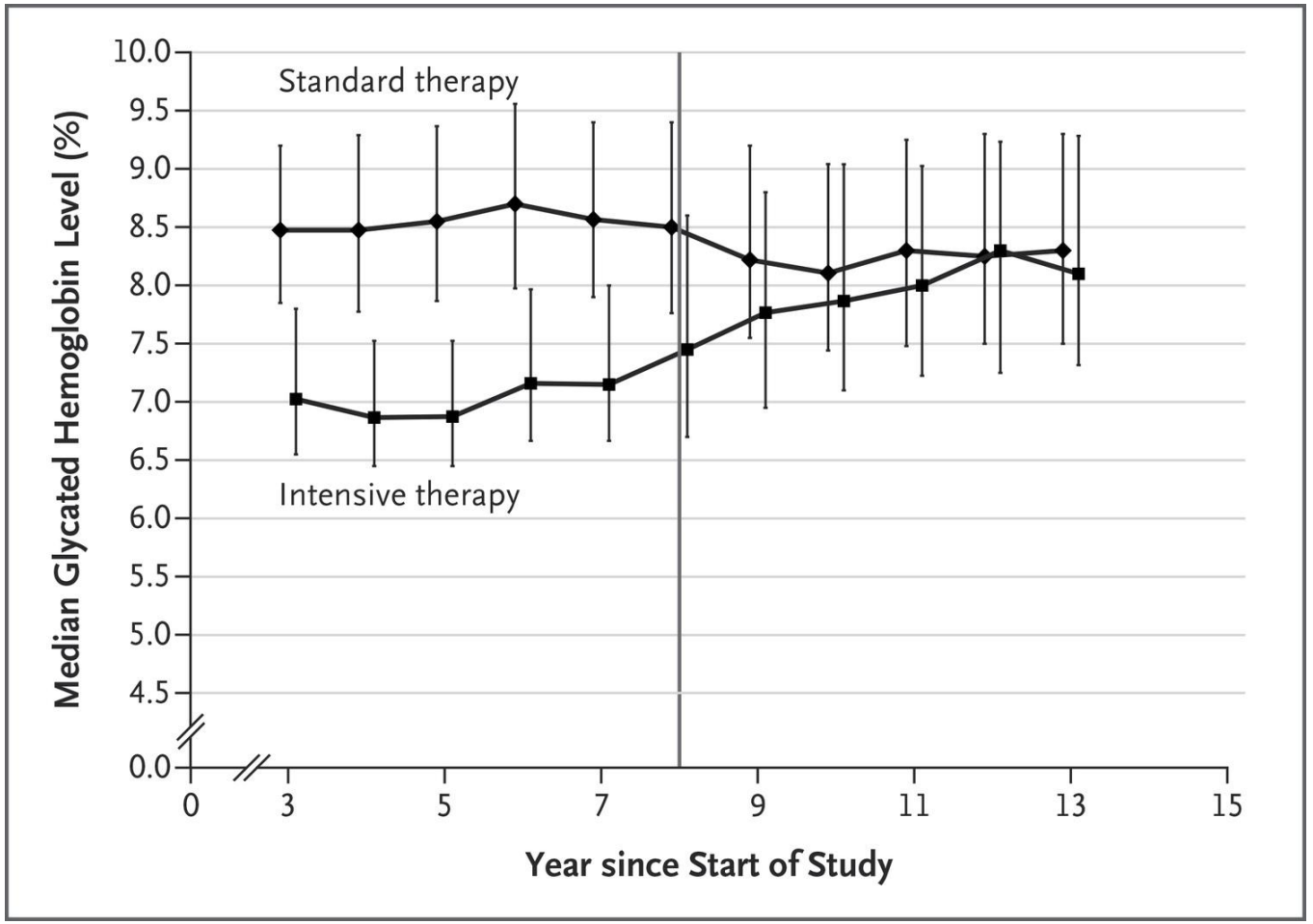
Change in HbA1c during the trial



Initial results

- No excess of cardiovascular mortality.
- No improvement of cardiovascular morbidity.
- No change in incidence of neuropathy or no change in rate of progression of neuropathy.
- But …improvement in progression from normal kidney function to microalbuminuria and from microalbuminuria to macroalbuminuria was significant favoring intensive arm .

years follow up of VADT cohort: 10 glycemic control



years Cardiovascular outcomes after 10

Table 2. Effect of Intensive Glucose Control on the Rate of Major Cardiovascular Events and Mortality.*

Outcome	Standard Therapy		Intensive Therapy		Hazard Ratio (95% CI)	P Value
	Events	Rate	Events	Rate		
	no. of participants/ total no.	*per 1000 person-yr*	*no. of participants/ total no.*	*per 1000 person-yr*		
Primary outcome: major cardiovascular event	288/688	52.7	253/703	44.1	0.83 (0.70–0.99)	0.04
Secondary outcomes						
Death from cardiovascular causes	83/818	11.3	74/837	10.0	0.88 (0.64–1.20)	0.42
Death from any cause	258/818	30.3	275/837	32.0	1.05 (0.89–1.25)	0.54

* The primary outcome was the time to the first major cardiovascular event (a composite of heart attack, stroke, new or worsening congestive heart failure, amputation for ischemic gangrene, or death from cardiovascular causes) and was analyzed in the survey cohort. Mortality outcomes were analyzed in the complete cohort.

Glycemic targets in diabetes: general consideration (ADA 2016)

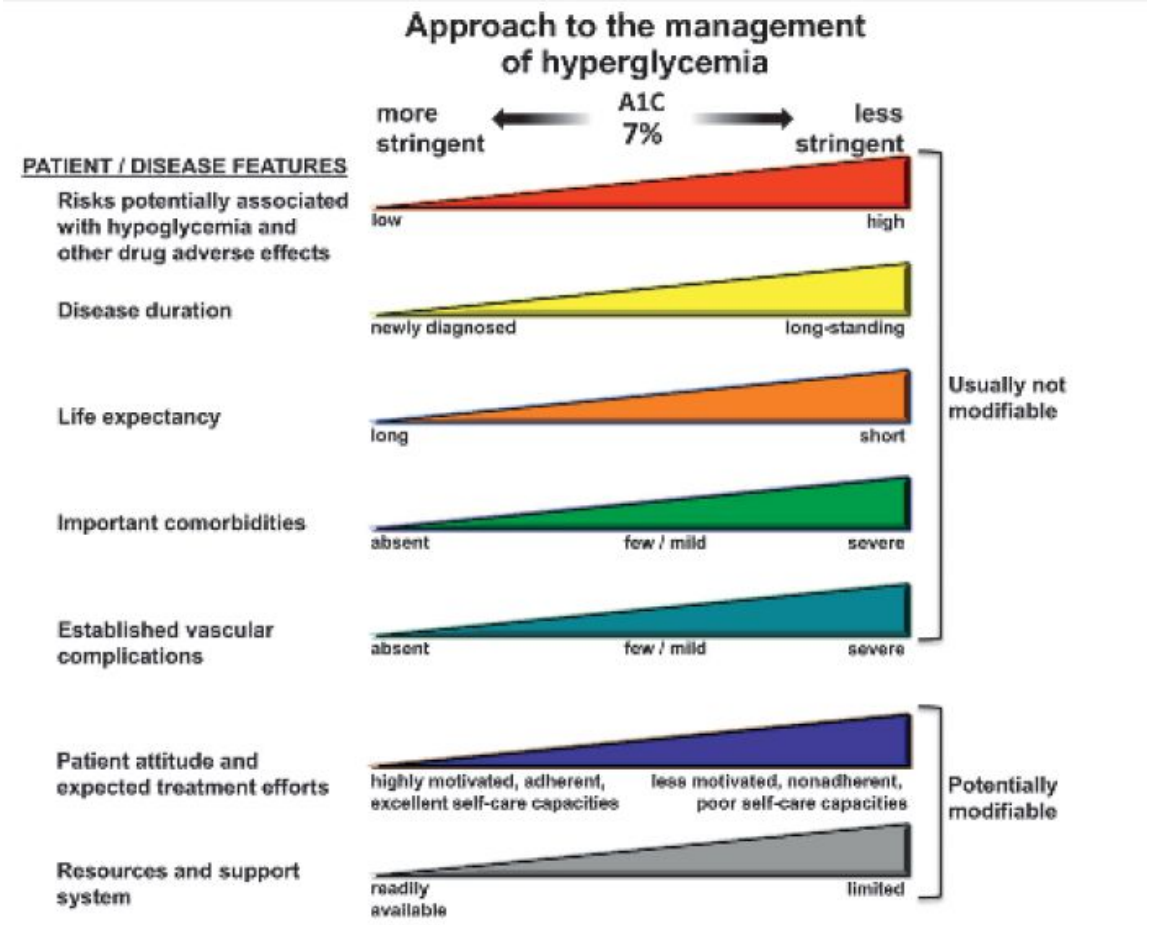
Table 5.2—Summary of glycemic recommendations for nonpregnant adults with diabetes

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.

Individualized treatment ADA 2016



Glycemic targets for treatment of pregnant women with type 1 and 2

- Fasting ≤90 mg/dL (5.0 mmol/L)
- One-hour postprandial ≤130–140 mg/dL (7.2–7.8 mmol/L)
- Two-hour postprandial ≤120 mg/dL (6.7 mmol/L)

Glycemic targets for treatment of pregnant women with type 1 and 2 diabetes

- Fasting ≤90 mg/dL (5.0 mmol/L)
- One-hour postprandial ≤130–140 mg/dL (7.2–7.8 mmol/L)
- Two-hour postprandial ≤120 mg/dL (6.7 mmol/L)

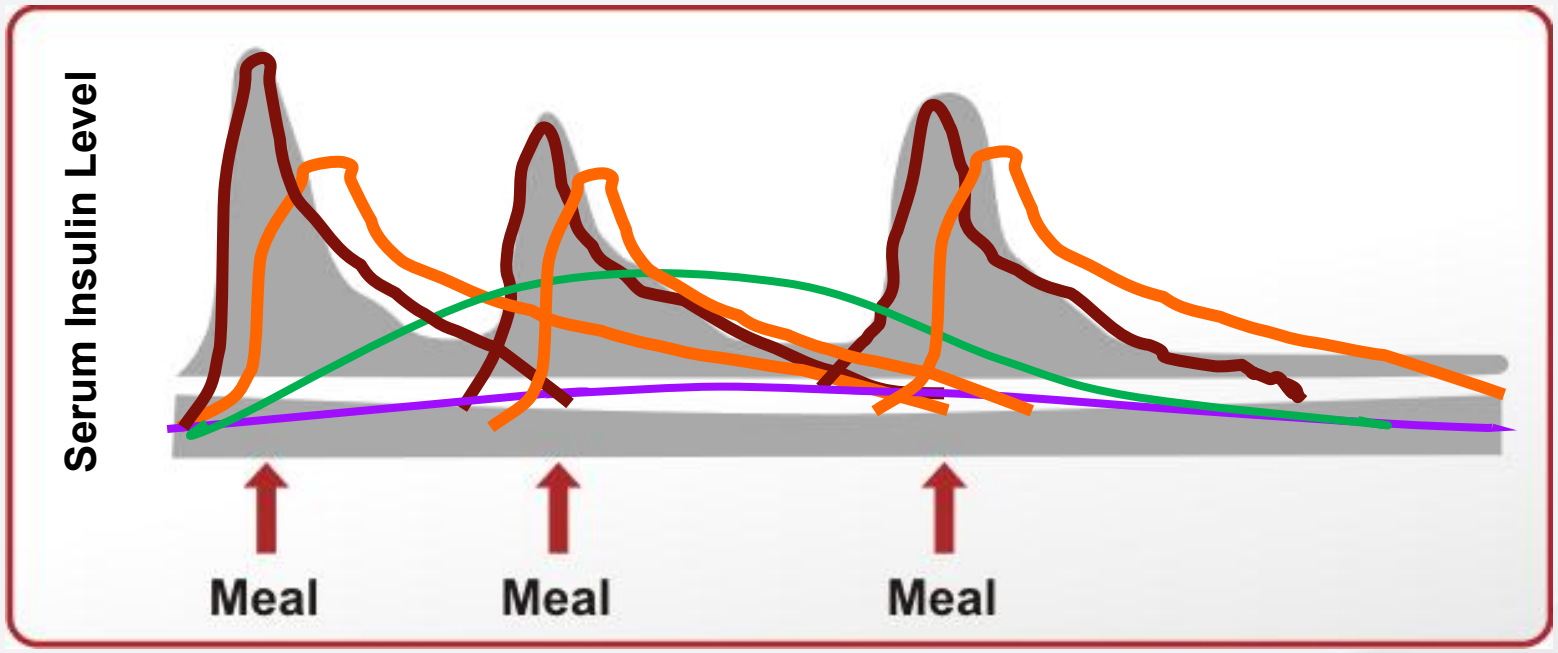
Optimal Hba1C :6-6,5% (avoid maternal hypoglycemia!)

Glycemic targets for women with GDM

- Fasting ≤95 mg/dL (5.3 mmol/L) and either
- One-hour postprandial ≤140 mg/dL (7.8 mmol/L) or
- Two-hour postprandial ≤120 mg/dL (6.7 mmol/L)

Type 1 insulin treatment
Concept of basal - bolus

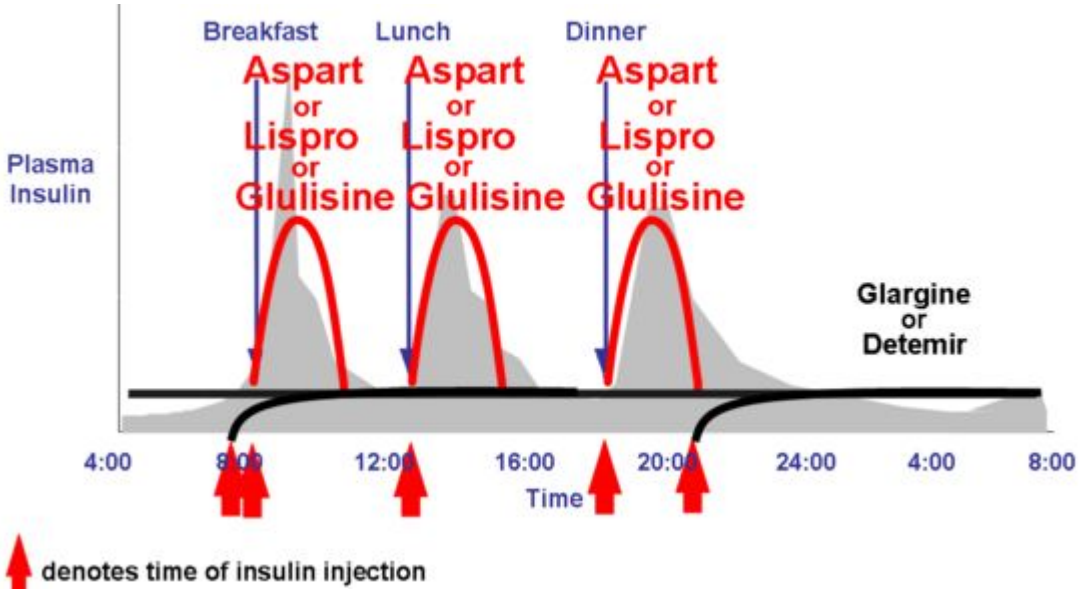
- Prescription of short and long acting insulins imitating physiologic insulin secretion.
- It is the modern method to treat type1 and advanced type 2 diabetes .
- Basal insulin injected once to time daily in order to control hepatic glucose output.
- Premeal insulin is added in order to prevent postprandial glycemia.



Insulin analogues

Insulin Preparation	Onset of Action	Peak of Action	Duration of Action
Meal Insulin			
Lispro	10-15 minutes	1-1.5 hours	3-5 hours
Aspart	10-15 minutes	1-2 hours	3-5 hours
Glulisine	10-15 minutes	1-2 hours	3-5 hours
Regular	30-60 minutes	2-4 hours	6-8 hours
Basal Insulin			
NPH	2.5-3 hours	5-7 hours	13-16 hours
Lente	2.5-3 hours	7-12 hours	Up to 18 hours
Ultralente	3-4 hours	8-10 hours	Up to 20 hours
Detemir	2-3 hours	6-8 hours	≈24 hours
Glargine	2-3 hours	No peak	≈24 hours
Degludec	—	No peak	>42 hours

Treatment scheme



Principles of type 2 treatment: (1)non –pharmacologic therapy

- Physical activity.

1.1Minimum 150 minutes weekly moderate intensity physical activity (50-70% of maximal heart rate) at least 3 days weekly .

1.2 Reduce sedentary time to 90 min.

1.3Minimum two session in week of resistance exercise : set of 5 exercise involving large muscle group.

Principles of type 2 treatment: (2)non –pharmacologic therapy

- Diet and carbohydrates
  1. **500-750 kcal/d deficit**:1200-1500 kcal /d for women,1500-1800 kcal/d for men:5% weight loss, ideally 7%
  2. **No ideal amount !!(but keep in with total advised caloric intake!).**
  3. Replace refined carbohydrate and added sugars with whole grains, legumes, vegetables, and fruits.
  4. **Keep in mind carb counting in IDDM.**

Principles of type 2 treatment: (3)non –pharmacologic therapy

- Diet and proteins
  1. **0.8 g/kg daily allowance.**
  2. **Enhance insulin response to carbohydrates.**
  3. **Don’t use protein- rich carbohydrate sources to revent hypoglycemia .**
- Diet and fat
  1. **Rich in monounsaturated fat** (Mediterranean style diet).
  2. 25-30 % caloric intake.
- Sodium in diet:

  Restrict to 2300 mg .
- Restrict alcohol consumption to one drink a day for adult woman and two drink a day to adult man .

Pharmacological treatment of glycemia type 2:drug classification

- Biguanides
- Secretagogues
- DPP4 inhibitors
- α- glycosidase inhibitor
- Thiazolidinedione
- GLP1 agonists
- SGLT2 inhibitors
- Insulin

Biguanides

- Metfomin(Glucomin,Glucophage)
- Preferred initial pharmacologic agent because of long standing record of efficacy and safety and lowering CV outcomes(UKPDS).
- Mechanism:

1. Decreased **hepatic gluconeogenesis** by **activation of AMP kinase.**
2. Other : lowering peripheral insulin resistance.

Metformin

- Half-life up to 3 hour.
- No metabolism ,excreted by kidney as active compound.
- May be safely continued down to glomerular filtrationrate (GFR) **of 45 mL/min/1.73m2** or even **30 mL/min/1.73 m2** with **reduced** dosage.
- Maximal dosage 2550 mg (usually 2-3 times daily.

Metformin toxicity and side effects

- Gastrointestinal (20-30%): start with lower dose with or after meals, make rotation with various formulation
- B12 deficiency.
- Lactic acidosis :(very uncommon) don’t use in advanced CKD, advanced liver disease, shock, severe infection ,alcoholism.

Secretagogues

- **Sulfonylureas**: bind to SUR1 site of inward rectified K_{ATP} channel on beta-cells :
- 2 generation

1. First generation: now abandoned because of cases of prolong hypoglycemia ,hyponatremia (chlorpropamide),transient leucopenia and thrombocytopenia (less than 1%) and multiple drug interaction.
2. Second generation: more safe.

nd generation sulfonylureas-2

Glipizide	5 mg	40 mg, div bid	5	Int: 12-24 hr	Metabolized by liver to inactive products that are excreted in the urine and, to a lesser extent, in the bile. Mild diuretic activity.
Glipizide extended release	5 mg	20 mg qd	5	Long: >24 hr	
Glyburide	2.5 mg	20 mg, div bid	5	Int: 16-24 hr	Metabolized by liver to weakly active and inactive products, excreted in urine and bile. Mild diuretic activity. Highest risk of hypoglycemia.
Micronized glyburide	3 mg	6 mg bid	3	Shorter	
Glimepiride	1 mg	8 mg qd	2	Long: >24 hr	Metabolized to inactive metabolites by liver, excreted in urine and bile.

Adverse effect : hypoglycemia ,weight gain

Secondary failure : sulfonylureas require functional beta -cells ,they lose efficacy with diabetes progression because of beta -cell failure.

Glinides

- Binding to distinct (from sulfonylurea) SUR 1 site
- Burst phase-1 insulin secretion
- In vitro- glucose dependent but in vivo not

Medications:

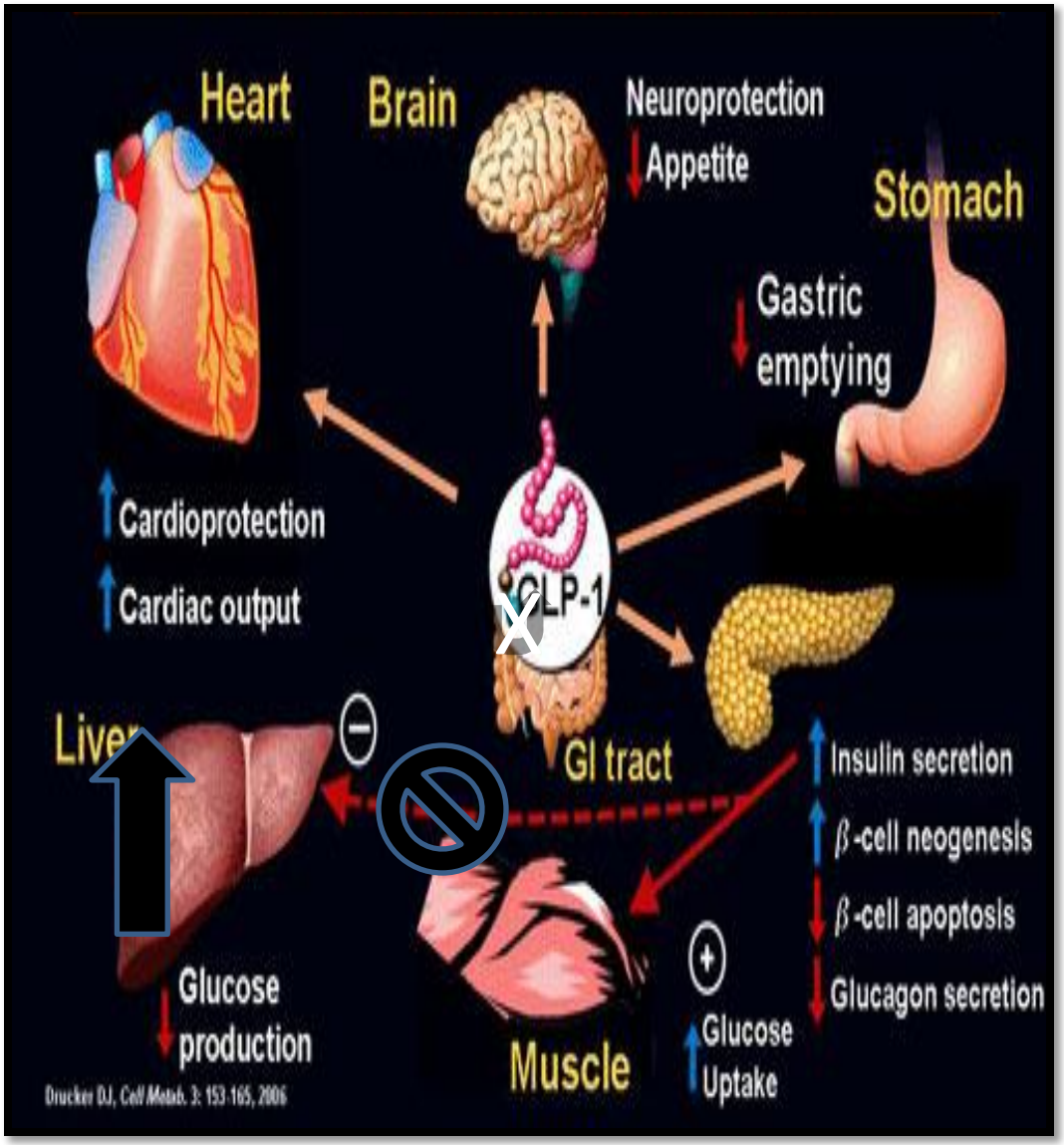
- Repaglinide(Novonorm)
- Nateglinide

Pharmacokinetics:

1. Rapid onset of action
2. Plasma half -life less than 1 hour
3. Intensive hepatic metabulism

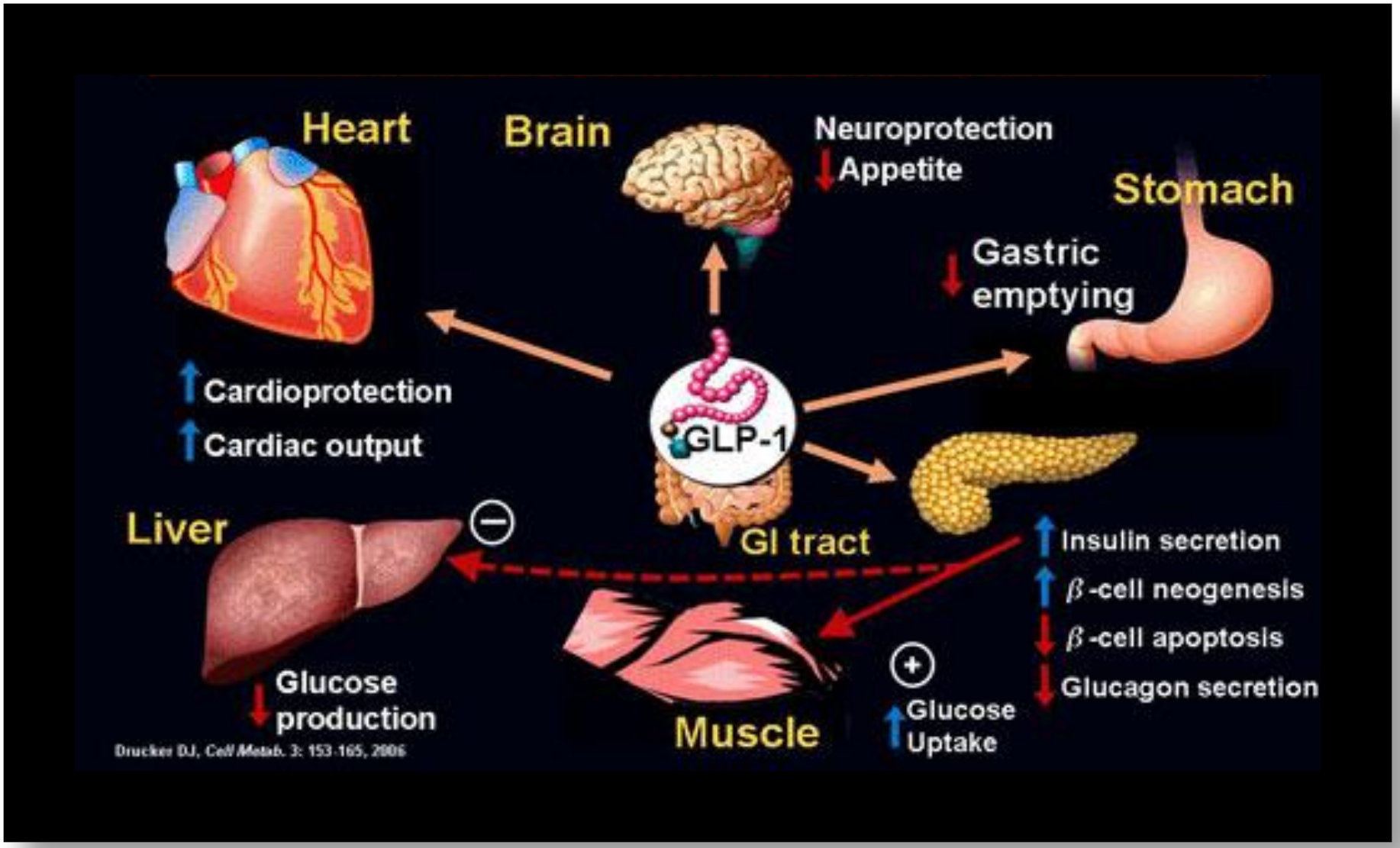
- Use for coverage postprandial glucose rise
- Suitable for CKD
- Repaglinide 3 times daily 15 minutes before meal: 0,5 mg to 4 mg 3 to 4 times daily
- Adverse effect : hypoglycemia ,weight gain

DPP-IV: ACTION



- Cleaves GLP-1
- *Results in decreased signal* to the pancreas—limiting insulin response.
- That in turn decreases the signal to the liver resulting in increased hepatic glucose production.
- HYPERGLYCEMIA

The Role of GLP-1



DPP4 inhibitors

Name			Class	Half-life	Dose (mg)	Use
Sitagliptin	Januvia	Merck	Short acting	8–24	100	Once daily
Alogliptin		Takeda	Short acting	12–21	25–50	Once daily
Linagliptin	aTrajent	Boehringer Ingelheim	Short acting	10–40	5	Once daily
Saxagliptin	Onglysa	BMS and AstraZeneca	Short acting	2–4	2.5–5	Once daily
Vildagliptin	Galvus	Novartis	Short acting	1.5–4.5	50	Twice daily

Very few side effects: mostly gastrointestinal
Neutral weight effect

GLP1 agonists(injectable agents)

- **Breakthrough in DM 2 treatment**
- Glycemic ,cardiovascular (LEADER study)benefit , **significant weight loss .**
- Side effects :Gastrointestinal side effects , weakness , mild tachycardia ,local injection reaction .

Exenatide (Byetta) 5-10 mg twice daily SC

Exenatide SR (Bydureon) 2mg once weekly SC

Liraglutide (Victoza)0.6 -1.8 mg once daily

Dulaglutide (Trulicity) 0,75 mg- 1.5 mg once weekly

α- glucosidase inhibitors

Primary mechanism of action	Inhibit digestion of polysaccharides from proximal small intestine
Requirements	Postprandial hyperglycemia
HbA1c efficacy	0.5–0.8%
Dosing	3 times a day
Side effects	Gastrointestinal, including flatulence

Abbreviations: HbA1c, glycated hemoglobin.

Acarbose (Prandase) max 100 mg *3/d
May have cardiovascular benefits (STOP – NIDDM trial)
Prohibited in advanced CKD

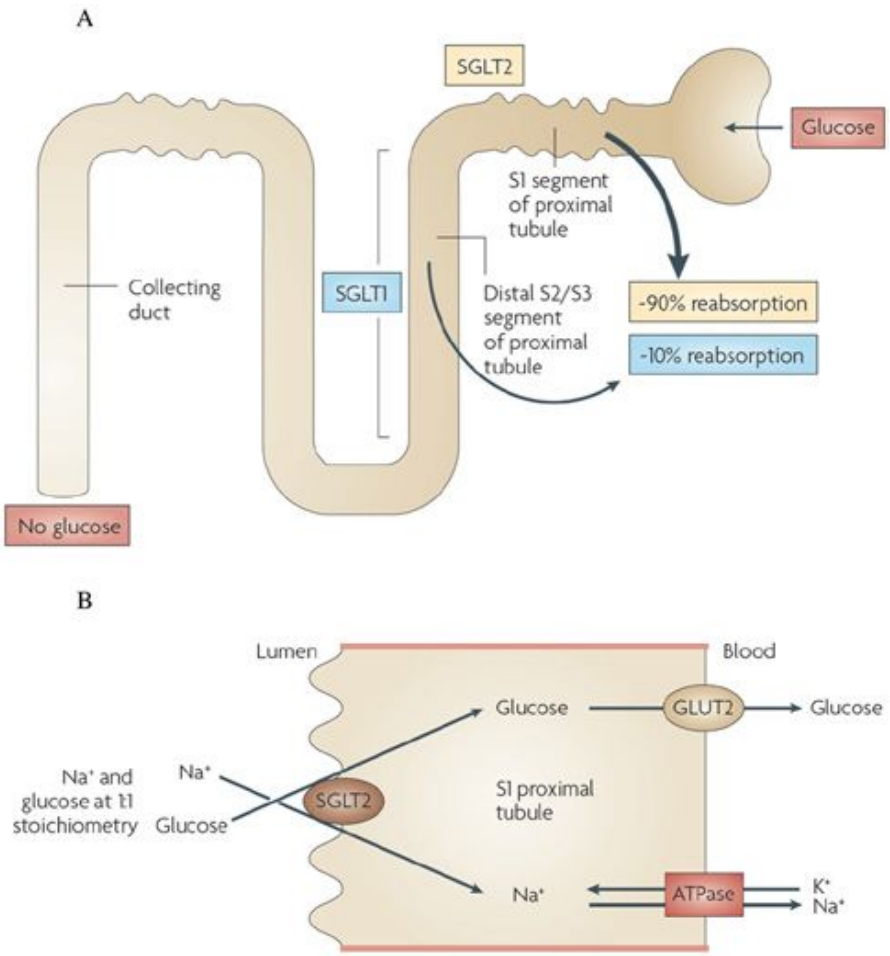
Thiazolidinediones

- Gamma- PPAR agonists.
- Increase of insulin sensitivity in adipose tissue skeletal muscle and liver.
- **Warning about potential increase of acute MI (ACCORD)**
- Side effects : weight gain because of fluid retention, worsening of heart failure ,anemia, increased risk of fracture.

Medication :

- Rosiglitazone (Avandia)4,8 ,16 mg once daily.
- Pioglitazone(Actos)15- 45 mg once daily.

SGLT2 inhibitors



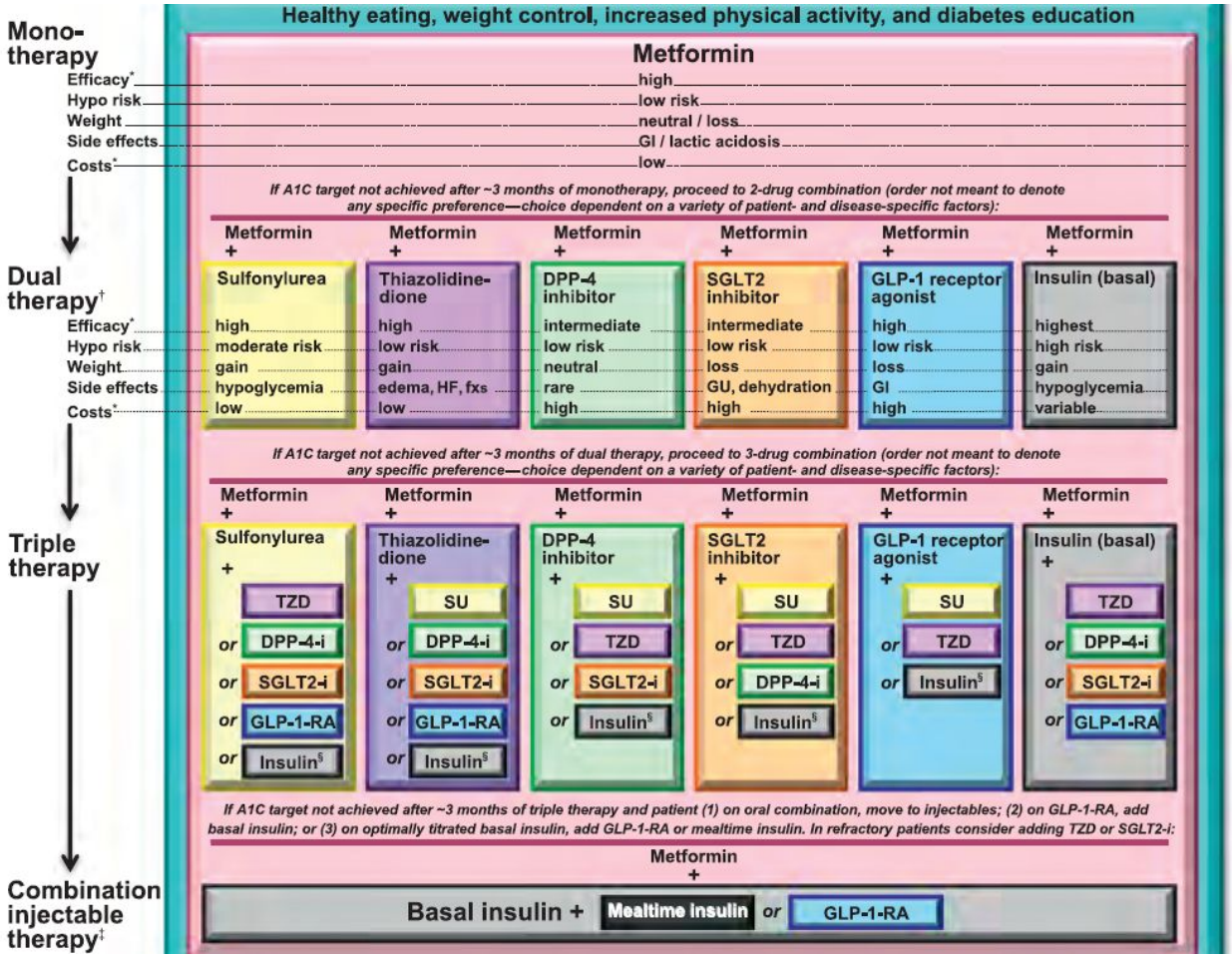
SGLT2 inhibitors medications

- Empafliglozin (Jardiance)10 mg ,25 mg
- Dapafliglozin(Forxiga) 10 mg

Positive effects :glucose lowering without hypoglycemia ,lowering of blood pressure and weight ,may be cardiovacular benefit(EMPA-REG),lowering proteinuria.

Side effects **: renal failure,polyuria,UTI and candidiasis and very ominous complication: normoglycemic DKA**

Algorithm ADA of glycemic treatment 2016



Comprehensive care of diabetes(ADA 2016)

- Stop smoking.
- Treat blood pressure to targets :less than140/90 mmHg: ADVANCE – BP , HOT study and ever ACCORD-secondary outcomes(stroke and proteinuria);
- Younger population, population with cardiovascular disease or risk factor, albuminuria, target may be less than 130/80mmHg.
- Unique role of ACE and ARB in treatment of diabetic population **especially with albuminuria** (more benefit in more than 300 mg /mg creatinine).

Statin treatment and diabetes

- Patients 40-75 without additional atherosclerotic cardiovascular disease(ACVD) risk factor- moderate intensity statin+ life style modification.
- Diabetes + ACVD= high potency statin
- Younger than 40 and older than 75 patient with additional ACVD factor = consider moderate to high potency statin.

Other recommendation

- Aspirin in 75-162 mg for secondary prevention.
- Primary prevention only for high ACVD risk(more then 10 % for 10 year).
- Scheduled vaccination against hepatitis B, seasonal against influenza and polyvalent pneumococcal vaccine in all adults aged ≥65.
- Seek for and treat comorbidities (e.g. OSA ,fatty liver).