

New guidelines for patients with abnormal glucose regulation (AGR) and CAD

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Management
of
cardiovascular disease
in
diabetes

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The prevalence of abnormal glucose regulation in patients with coronary artery disease across Europe:

The Euro Heart Survey on Diabetes and the Heart

2.107 patients with acute clinical condition and 2.854 elective patients: 31% (32 and 30%) had known – mostly type 2 (93%) – diabetes.

Of the remaining patients, provided an oral glucose tolerance test (OGTT) was performed (56%), the glucometabolic state was as follows:

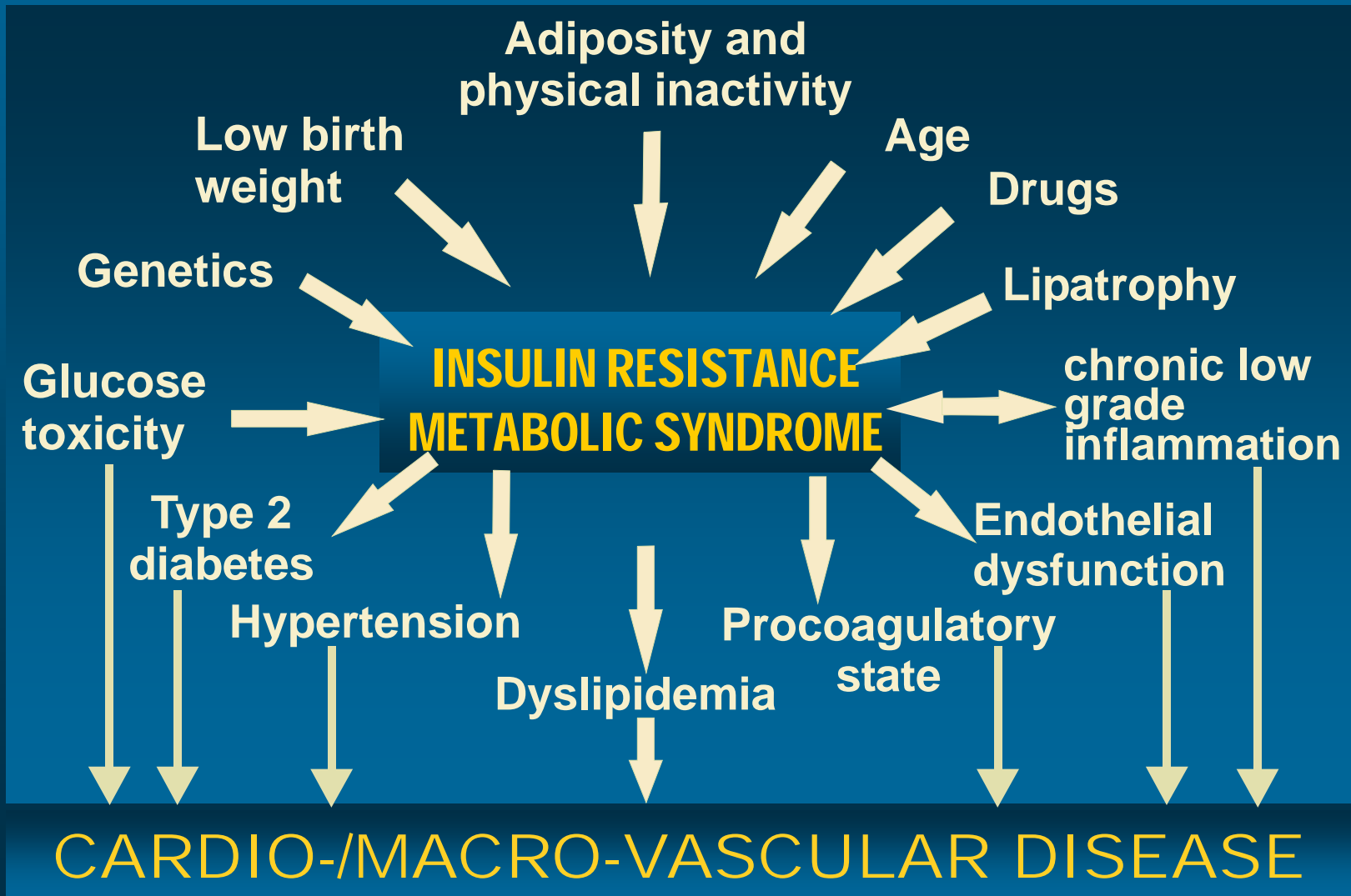
		Normal	IFG	IGT	new Diabetes
acute	patients	42%	4%	32%	22%
elective		49%	5%	32%	14%

Conclusion: The **majority** (approx. **70%**) of both acute and elective patients **has** known or previously unknown **diabetes, IGT or IFG. Without OGTT two thirds** of patients with abnormal glucose regulation **are missed**.

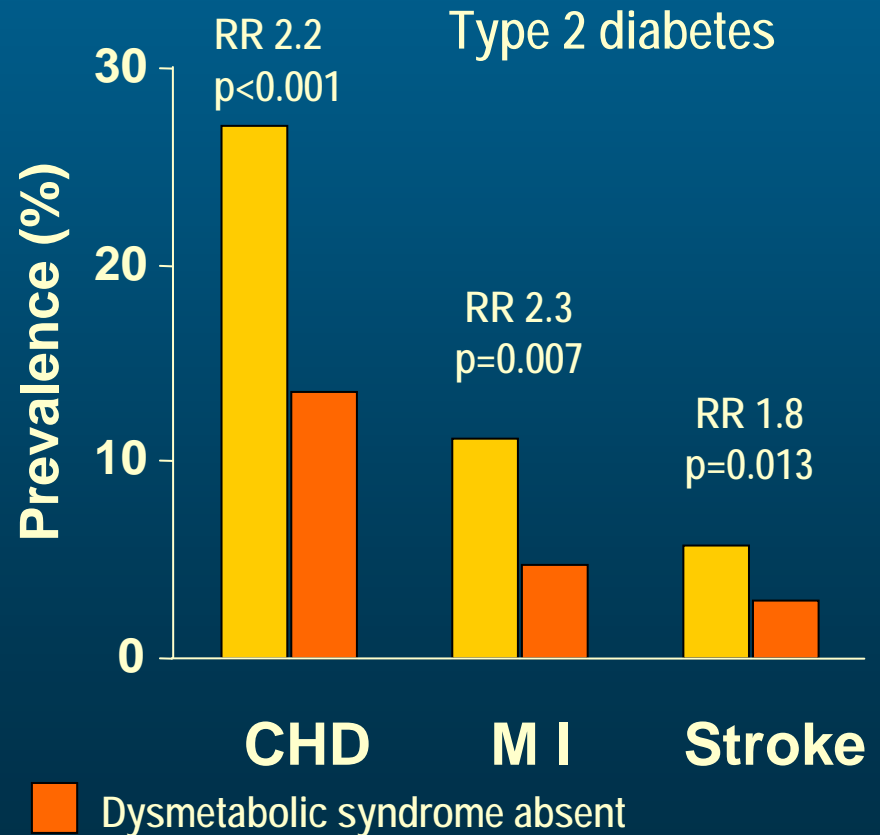
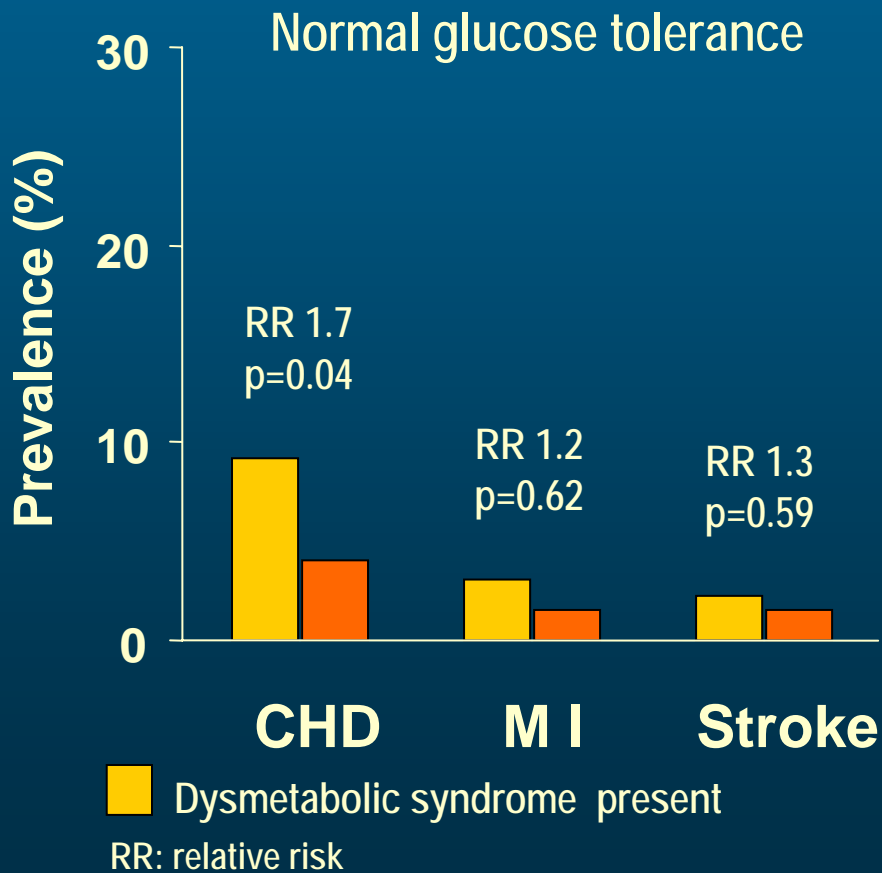
Treatment objectives for patients with AGR or metabolic syndrome, respectively, and CAD

- Prevention of diabetes (manifestation)
- Prevention of new major cardiovascular events

Metabolic syndrome / Insulin resistance: causes and associated disease



Type 2 diabetes amplifies the adverse effects of the dysmetabolic syndrome



Campaign „Enduring Freedom“ from complications in Type 2 diabetes

Below 6,5 and 3x below 100!

i.e. below 6,5% HbA1c

below 100 mg/dl fasting blood glucose

below 100 mg/dl LDL-Cholesterol

below 100 mmHg mean blood pressure

(eg. below 120/80)

The Steno 2 Study

n=160 T2 diabetics with microalbuminuria
age at baseline 55(\pm 7.2)yr
follow-up 7.8(\pm 0.3)yr

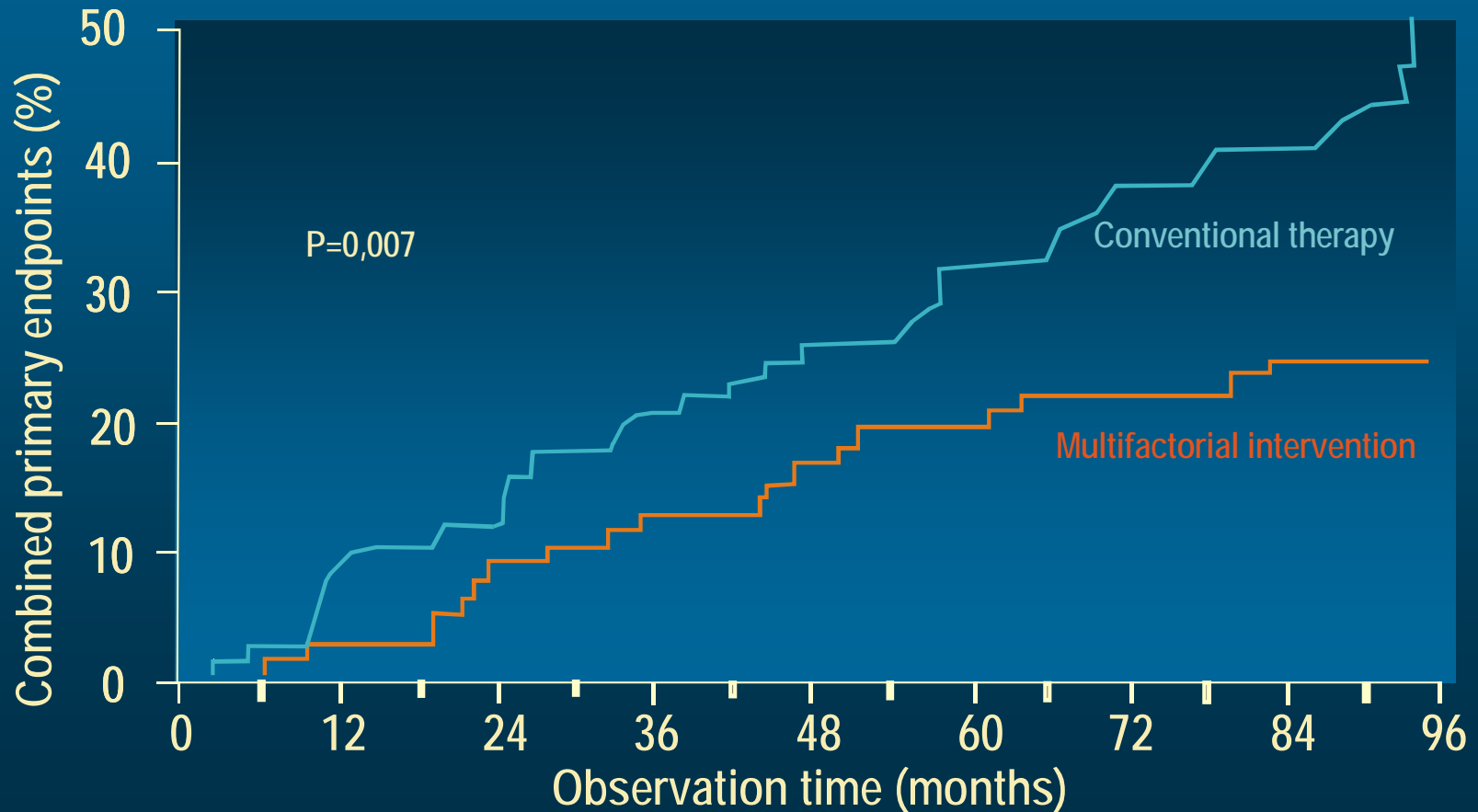
Targets

HbA1c <6.5% vs 7.5%
BP <140/85 vs <160/95mmHg
Chol <190 vs <250mg/dl
TG <150 vs <195mg/dl

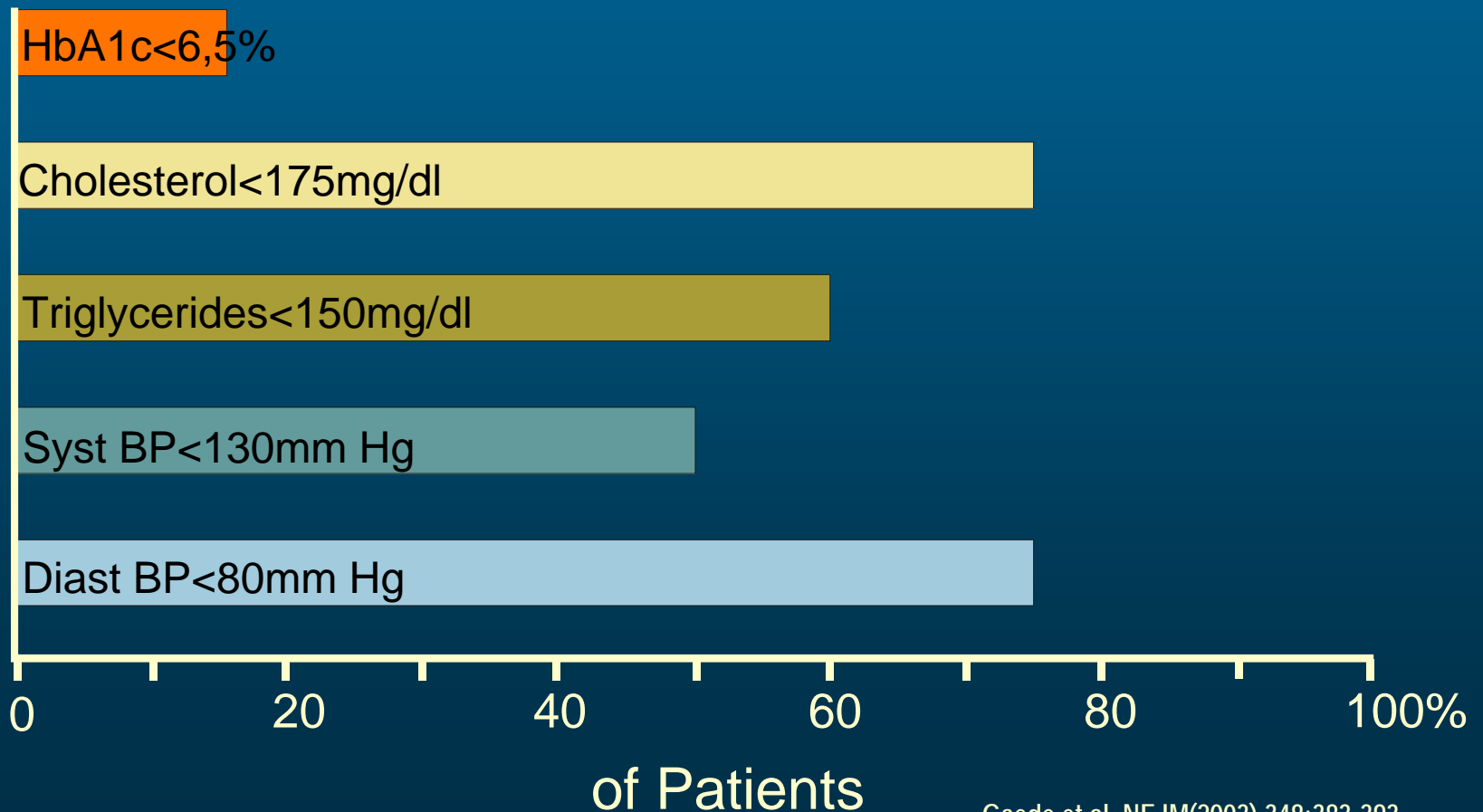
Intervention

Metformin, Glipizide, bedtime NPH
ACE inhib. or/and AT1-blocker
Statin
+ Fibrates, if needed
Aspirin

Multifactorial Intervention Reduces CV – Events in Type 2 Diabetics: The Steno 2 Study



Percentage of patients achieving set intensive targets in the Steno 2 Study



Guidelines for patients with AGR & CAD

- Treatment according to risk assessment (metabolic syndrome)
- Lifestyle and comprehensive management as basis

IDF consensus definition (2005)*

Central Obesity	
Waist circumference – ethnicity specific*	
– for Euroids: Male ≥ 94 cm Female ≥ 80 cm	
plus any two of the following:	
Raised Triglycerides	≥150mg/dL (1.7mmol/L) <i>or specific treatment for this lipid abnormality</i>
Low HDL Cholesterol	<40mg/dL (1.03 mmol/L) in males <50mg/dL (1.29 mmol/L) in females <i>or specific treatment for this lipid abnormality</i>
Raised blood pressure	Systolic : ≥130 mmHg or Diastolic : ≥85 mmHg or <i>Treatment of previously diagnosed hypertension</i>
Raised fasting plasma glucose (FPG)	FPG ≥100 mg/dL (5.6 mmol/L) or Previously diagnosed type 2 diabetes <i>If above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define presence of the syndrome.</i>

* For country/ethnic specific waist circumference values, see Alberti KGMM., IDF Consensus on the Metabolic Syndrome: Definition and Treatment, presented at 1st International Congress on Prediabetes and the Metabolic Syndrome, Berlin, 14 April 2005, available on-line: <http://www.idf.org/webcast>

Implementation of a healthier lifestyle

- Increase of physical activity
(e.g. 30 min. walking 5 times / week)
- Regulation (reduction) of body weight
(e.g. by about 5 kg from baseline)

Prevention of Type 2 Diabetes – Studies in Impaired Glucose Tolerance

Study	Journal/year	Description	Risk Reduction (%)
Da Qing ¹	Diabetes Care 1997	Diet and/or Exercise	31–46
Diabetes Prevention Study (DPS) ²	N Engl J Med 2001	intensive Life Style	58
Diabetes Prevention Program (DPP) ³	N Engl J Med 2002	Metformin Life Style	31 58

¹Pan XR, et al. *Diabetes Care* 1997;20:537–44.

²Tuomilehto J, et al. *N Engl J Med* 2001;344:1343–50.

³Knowler W, et al. *N Engl J Med* 2002; 346:393–403.

Intervention studies of type 2 diabetes

	Conversion to diabetes (%) and relative risk reduction vs. controls							
Study	Follow-up	Controls # (%)	Diet (%)	Exercise (%)	Diet + exercise (%)	Met-formin (%)	Acar-bose (%)	Orli-stat (%)
Da Qing IGT and Diabetes Study	6.0	67.7	43.8 (-31)	41.1 (-46)	46.0 (-42)			
Finnish Diabetes Prevention Study	3.2	23.0			11 (-58)			
US Diabetes Prevention Program	2.8	28.9			14.4 (-58)	21.7 (-31)		
STOP-NIDDM	3.3	42.0					32 (-25 up to -36*)	
Xendos Study	4.4	9.0						37.3

usual national recommendations for life-style-modification

* two consecutive positive oGTT

Randomized, controlled studies with prevention of diabetes as secondary endpoint

		<u>RR/%</u>	<u>ARR/%</u>	<u>NNT</u>
HOPE	Ramipril/Placebo	33	1.8	55
CAPP	Captopril/Thia./Beta.	12	0.8	125
ALLHAT	Lisinopril/Chlorth.	30	3.4	29
LIFE	Losartan/Atenolo	25	2	50
VALUE	Valsartan/Amlodipin	23	3.3	30
CHARM	Candesartan/Placebo	22	1.4	71



Development of first cardiovascular events

Cardiovascular event	No. of patients		Risk red. (%)	p					
	Ac (n=682)	PI (n=686)		0	0.5	1.0	1.5	2.0	
Coronary heart disease									
myocardial infarction	1	12	91						0.0226
angina	5	12	55						0.1344
revascularisation	11	20	39						0.1806
cardiovascular death	1	2	45						0.6298
Congestive heart failure	0	2	—						—
Cerebrovascular accident/ stroke	2	4	44						0.5061
Peripheral vascular disease	1	1	—						0.9255
Any prespecified cardiovascular event	15	32	49						0.0326

Favours
acarbose

Favours
placebo

Medicinal start for a comprehensive therapy of the Metabolic Syndrome

- Metformin:
(UKPDS, DPP) diabetes ↓, obesity ↓, blood pressure ↓
- Acarbose:
(STOP-NIDDM, Metaanalyse) diabetes ↓, blood pressure ↓, CVD ↓, lipids ↓
- Ramipril:
(HOPE) CVD ↓, diabetes ↓
- Pravastatin:
(WOSCOPS) CVD ↓, diabetes ↓
- Losartan:
(Life) diabetes ↓, stroke ↓, CVD ↓
- Niaspan:
(HATS) CVD ↓, HDL-C ↑, TG ↓

Ongoing Studies

DREAM

5 yrs.

4000 IGT

DESIGN

Ramipril
Rosiglitazone
Placebo

2009

NAVIGATOR

6 yrs.

7500 IGT

Nateglinide
Valsartan
Placebo

2007

ORIGIN

5 yrs.

10000 IGT,IFG,T2D

Standard therapy
Lantus
Fish oil

2008



Primary objectives

Incidence of Diabetes
CV event rate

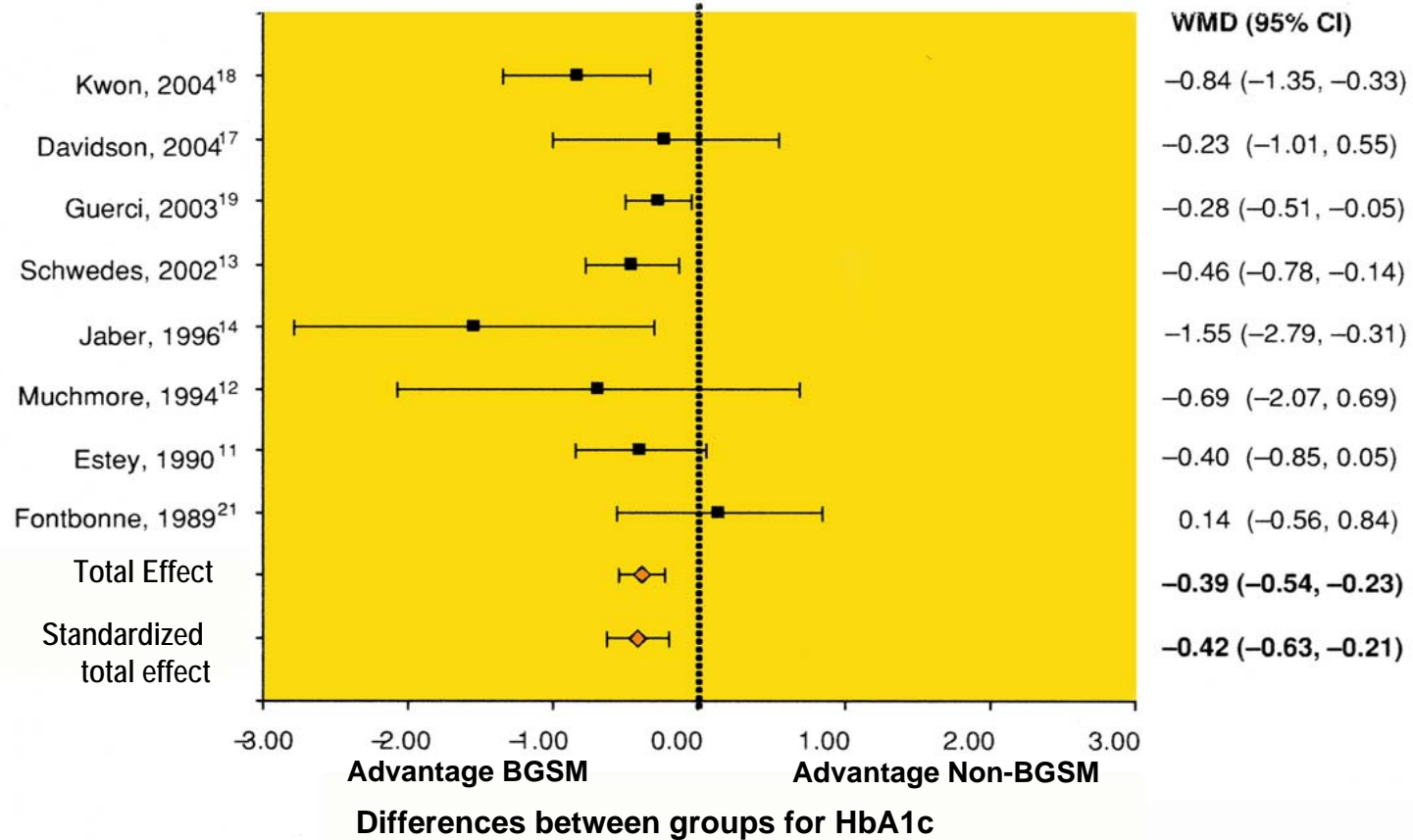
Regulation of body weight

- Restriction of calorie intake to about 1.500 kcal / d
- Restriction of fat intake to 30 (-35) % of total energy uptake
- Uptake of 10% of energy as mono-unsaturated fatty acids (e.g. olive oil)
- Avoidance of transfats
- Fibre uptake of 30 g / d
- Avoidance of mono- and disaccharides in liquids

Closing the gap between the complex needs of comprehensive management and the challenges in daily life:

- Intensive counselling is mandatory
- Structured therapy (polypharmacy as a problem!)
including training classes
- Self-monitoring of blood glucose and blood pressure
- Self-monitoring diary
- Quality management and certification
- Outcome evaluation
- Incentives for patient and physician

Effect of Blood Glucose Self Monitoring (BGSM) on HbA1c in Type-2-Diabetics without Insulin Therapy



Approach to care for abnormal glucose regulation in CAD patients

Consult endocrinologist / diabetologist for

- structured education
- blood glucose self monitoring (also pp glucose)
- appropriate nutrition counselling
- pharmacotherapy discussing pros and cons

	Benefits	Caveats
insulin	yes	
metformin	yes	impaired kidney function
sulfonylureas	yes	Cardiac K-channels ?
alpha-glucosidase-inhibitors	yes	
glitazones	?	CHF
glinides	?	

Mean efficacy of pharmacological treatment options in patients with Type 2 diabetes

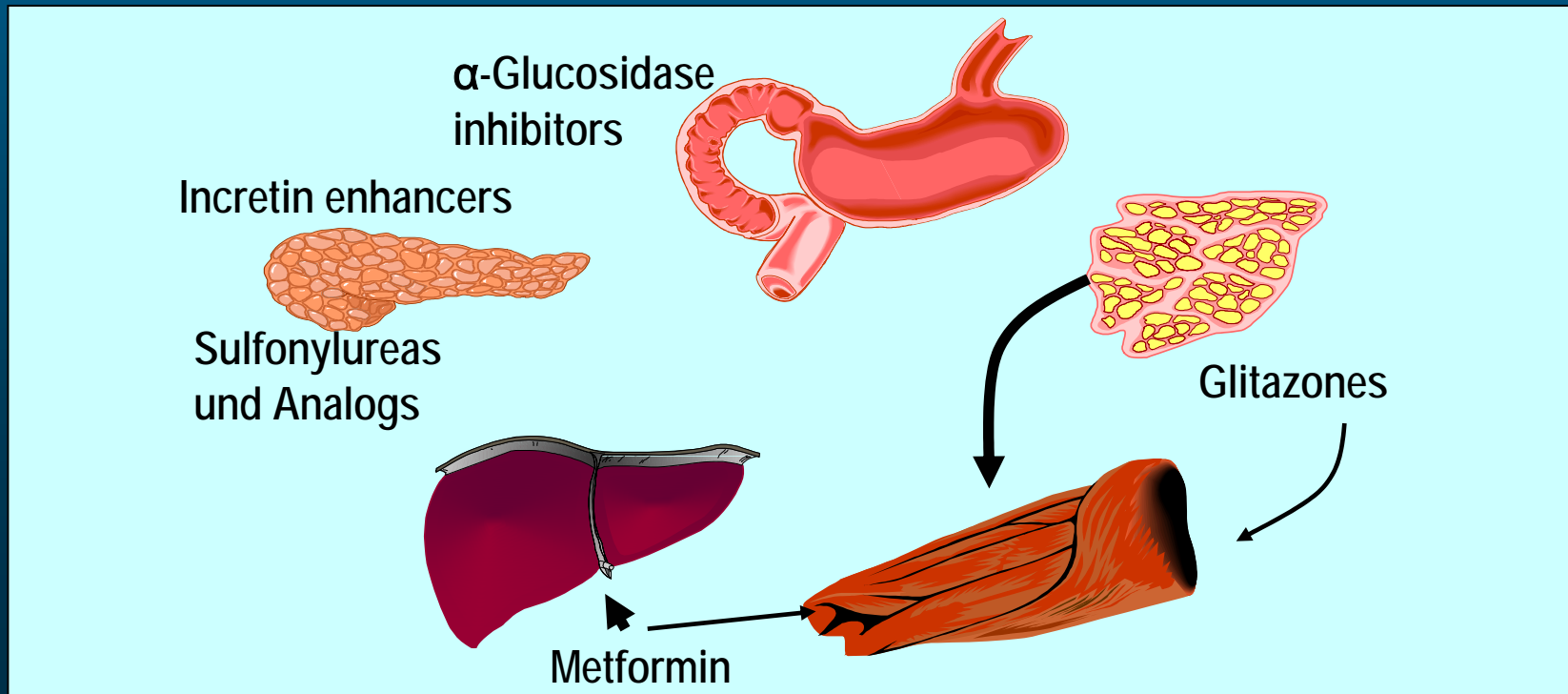
Drug	Mean lowering of initial HbA _{1c} (%)
Alpha-glucosidase inhibitors	0.5-1.0
Biguanides	1.0-1.5
Glitazones	0.5-1.5
Sulphonylurea derivatives	1.0-1.5
Glinides	1.0-1.5
Insulin	1.0-2.0

Type 2 diabetes

**early combination therapy
(to maximise efficacy,
to minimise side effects);
don't wait for failure !**

Arguments in favor of early combination therapy:

- additive efficacy through different mode of actions
- therapy of different abnormalities
- at medium dose 70-80% of maximum effect → less side effects



Policy of selecting the appropriate antidiabetic therapy according to the metabolic situation

Postprandial hyperglycaemia

alpha-glucosidase inhibitor,
short acting sulphonylurea,
Glinide, short acting regular
insulin or insulin analog, respectively

Fasting hyperglycaemia

biguanide,
long acting sulphonylurea,
glitazone, long acting insulin or
insulin analog, respectively

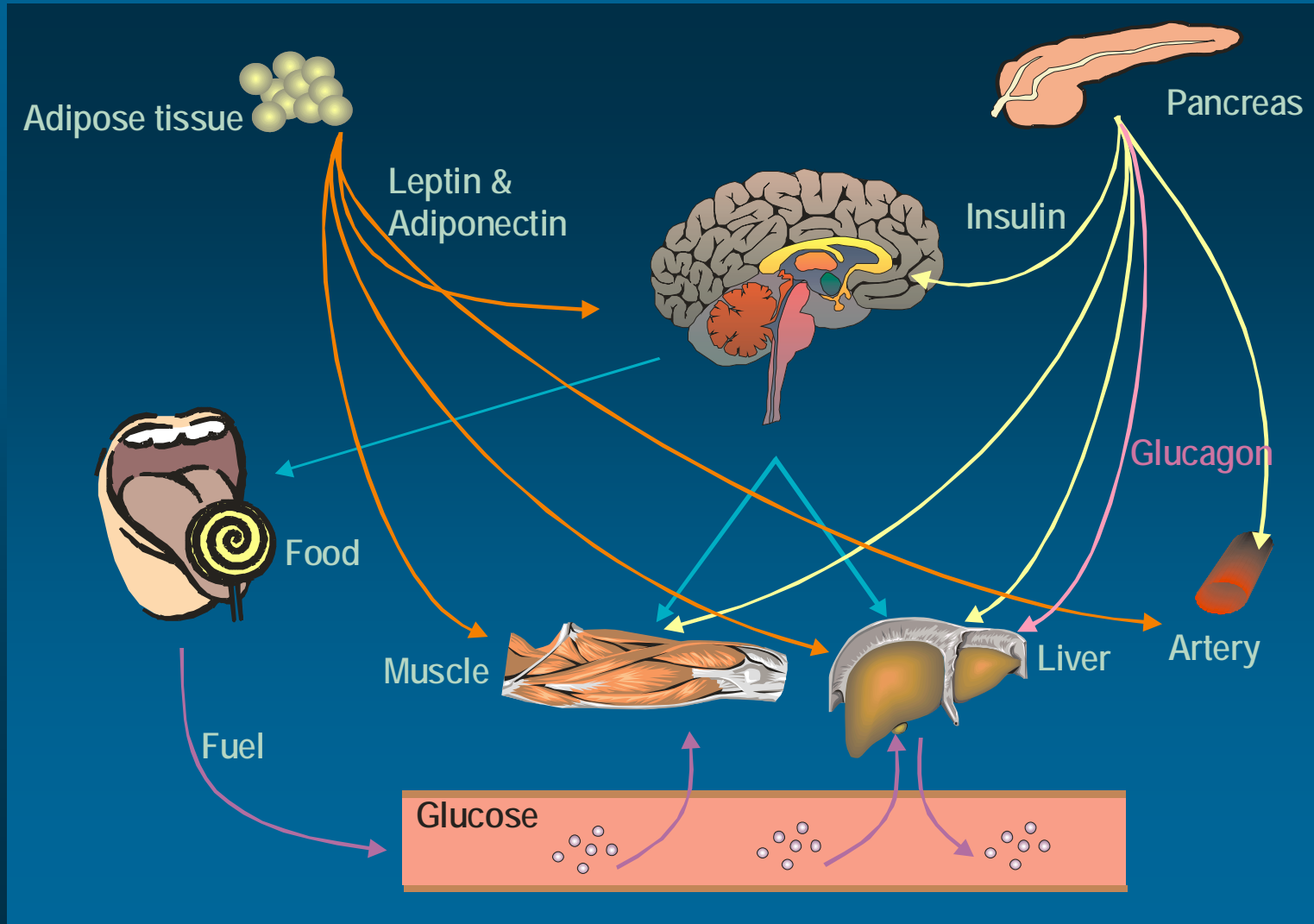
Insulin resistance

biguanide, glitazone,
alpha-glucosidase inhibitor

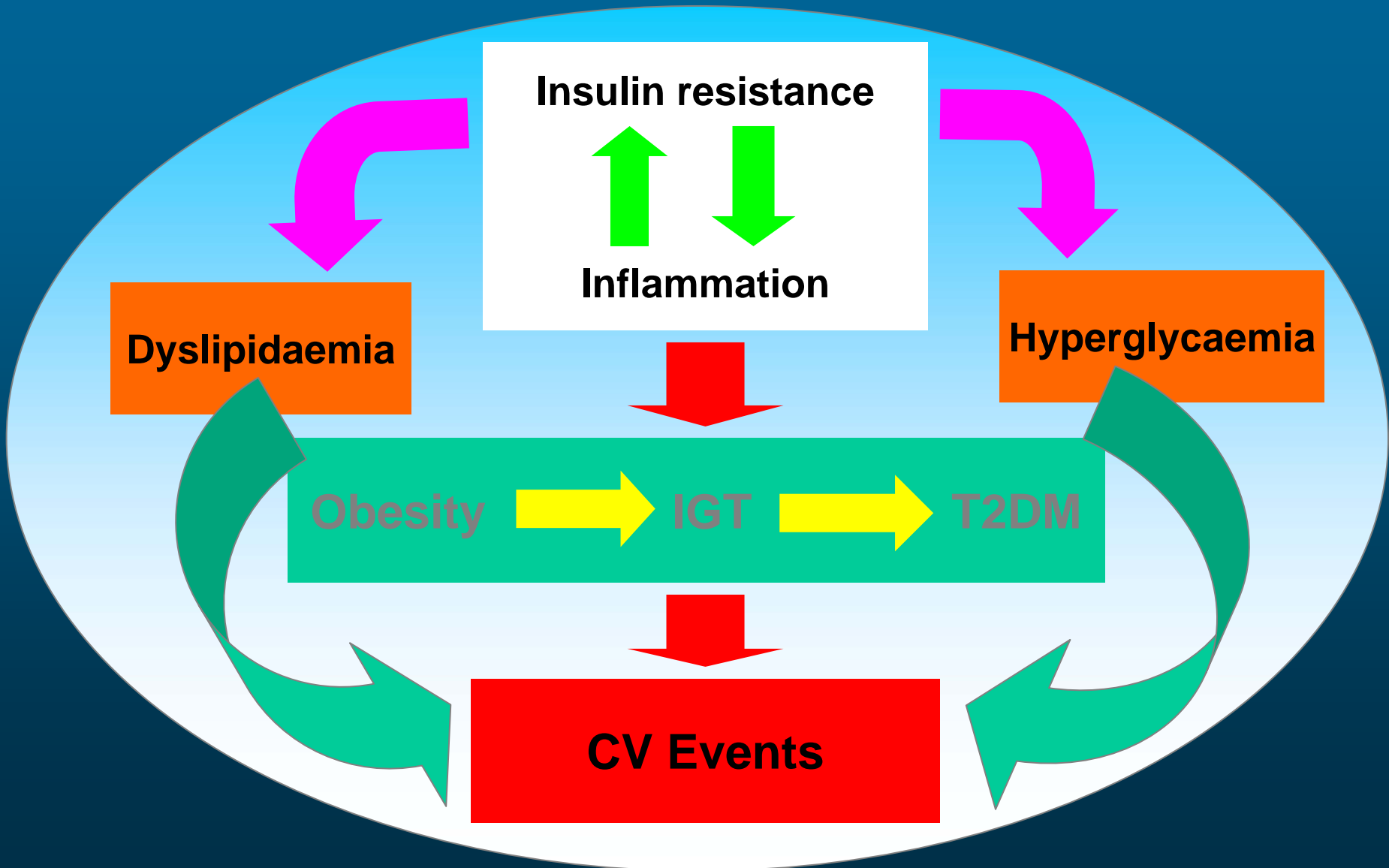
Insulin deficiency

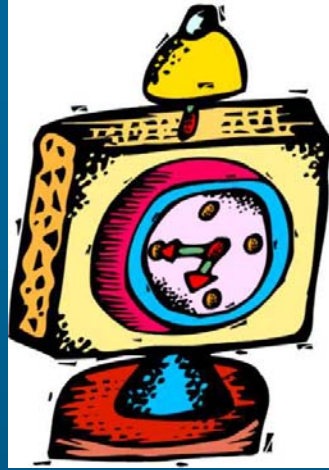
sulphonylurea,
glinide, Insulin

Pathogenetic key organs and hormones in Type 2 diabetes



'Common soil' mechanisms are operating.....





„The clock starts ticking before diabetes is diagnosed.“

SM Haffner

Diabetes and Atherosclerosis
develop in parallel.