

Corso di Aggiornamento
OMCeO BG via G. Manzù 25 - Bergamo

Fisiopatologia del DMT2 e potenzialità dei farmaci innovativi

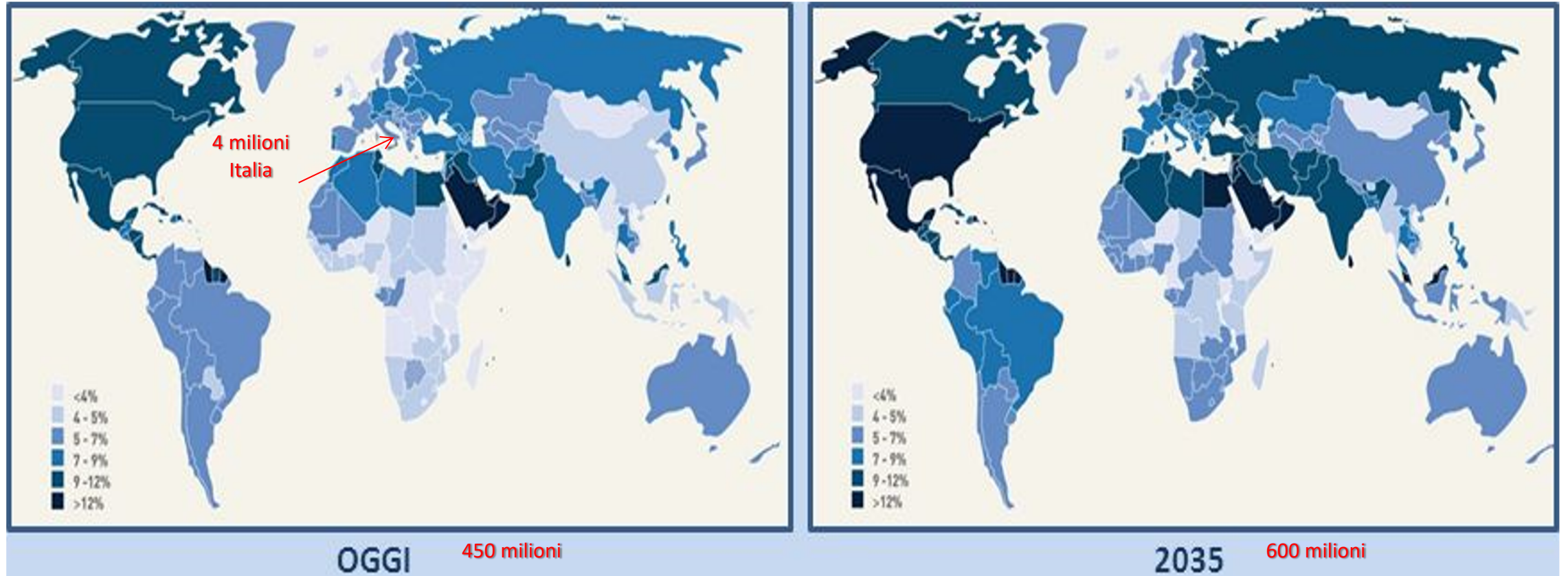
Marco Mirani

Humanitas Research Hospital – Rozzano (MI)

2 Febbraio 2022

HUMANITAS
RESEARCH HOSPITAL

Diabete Mellito



Diabete Mellito (classificazione)

un contenitore di malattie diverse

Tipo 2

LADA

Tipo 1

Tipo 3 ?

MODY 1-2-3-4-5-6

Secondario

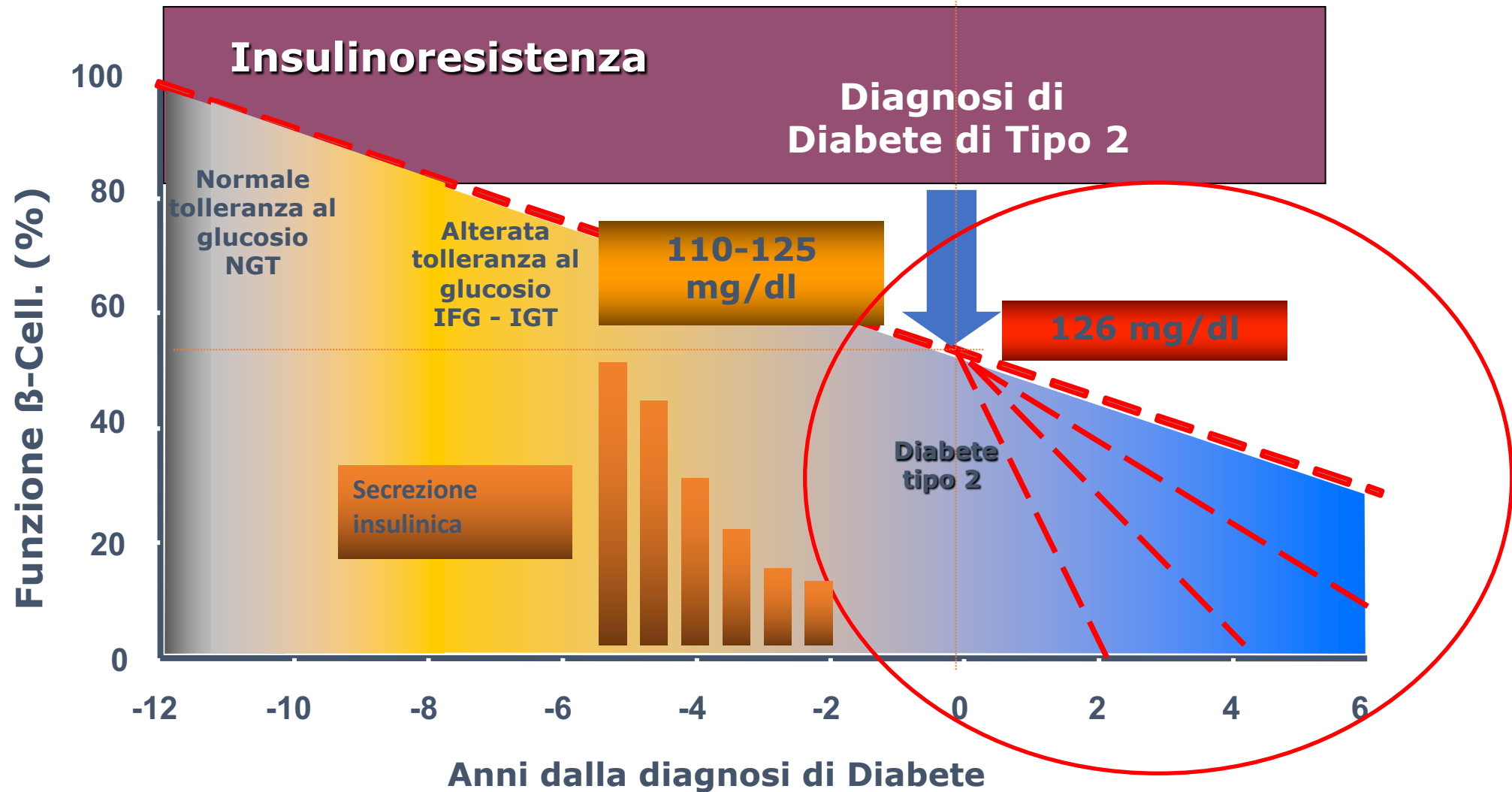
Classificazione del diabete

- *Diabete tipo 1*
 - * *immunomediato*
 - * *idiopatico*
- *Diabete tipo 2*
 - * *insulino-resistenza*
 - * *insulino-deficienza*
- *Diabete gestazionale*
- *Altri tipi specifici*

Prediabete:

IFG (Alterata glicemia a digiuno) e IGT (Ridotta tolleranza al glucosio)

Diabete Mellito Tipo 2: Storia Naturale



Adapted from UK Prospective Diabetes Study Group (UKPDS 16).
Diabetes. 1995;44:1249-1258.

Lilly Lecture 1987

The Triumvirate: β -Cell, Muscle, Liver

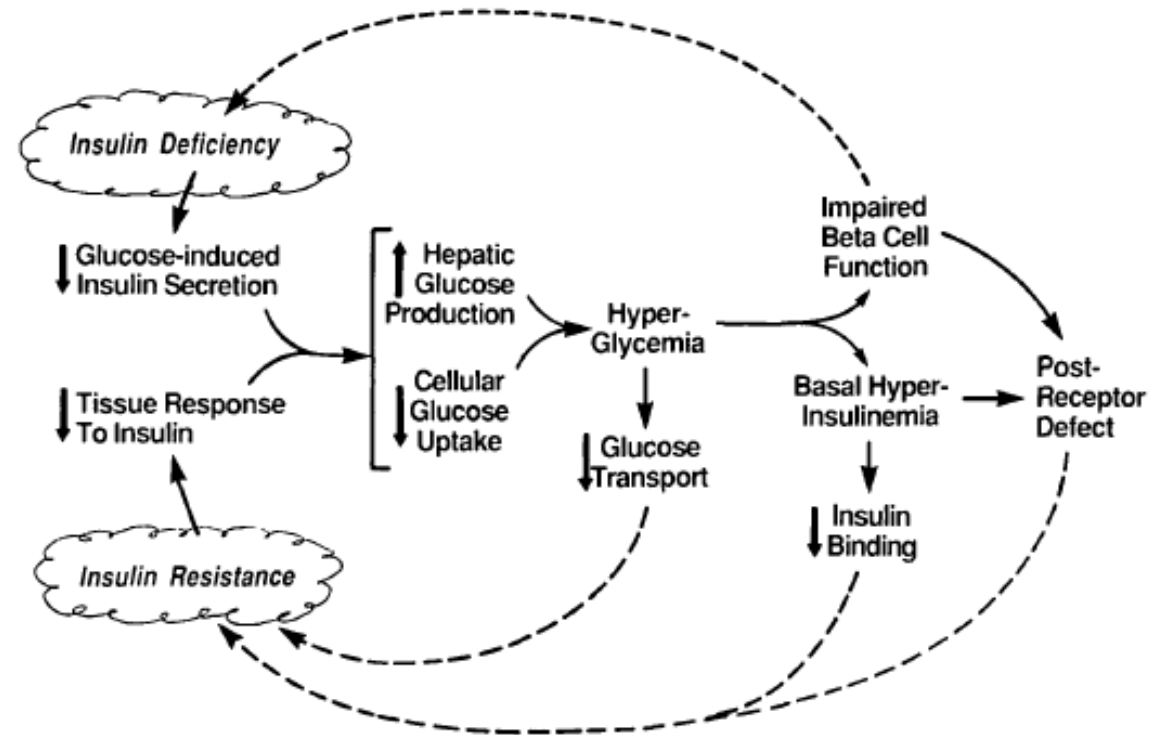
A Collusion Responsible for NIDDM

RALPH A. DeFRONZO

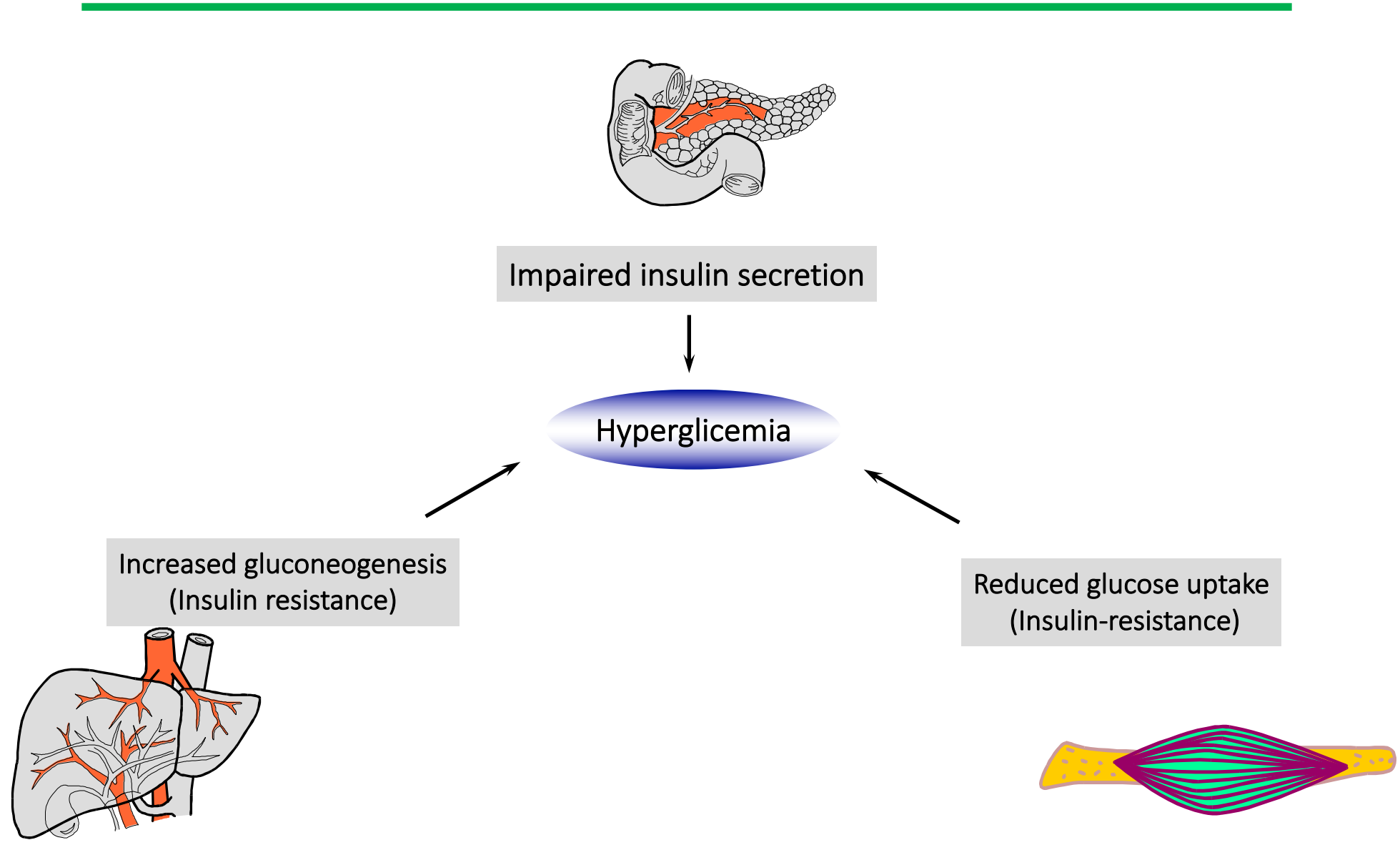
DIABETES, VOL. 37, JUNE 1988

Factors responsible for maintenance of normal glucose homeostasis in humans

Insulin secretion
Stimulation of glucose uptake
 Peripheral tissues (muscle)
 Glucose oxidation
 Nonoxidative glucose disposal (glycogen synthesis, glycolysis)
 Splanchnic tissues (liver plus gut)
Suppression of hepatic glucose production



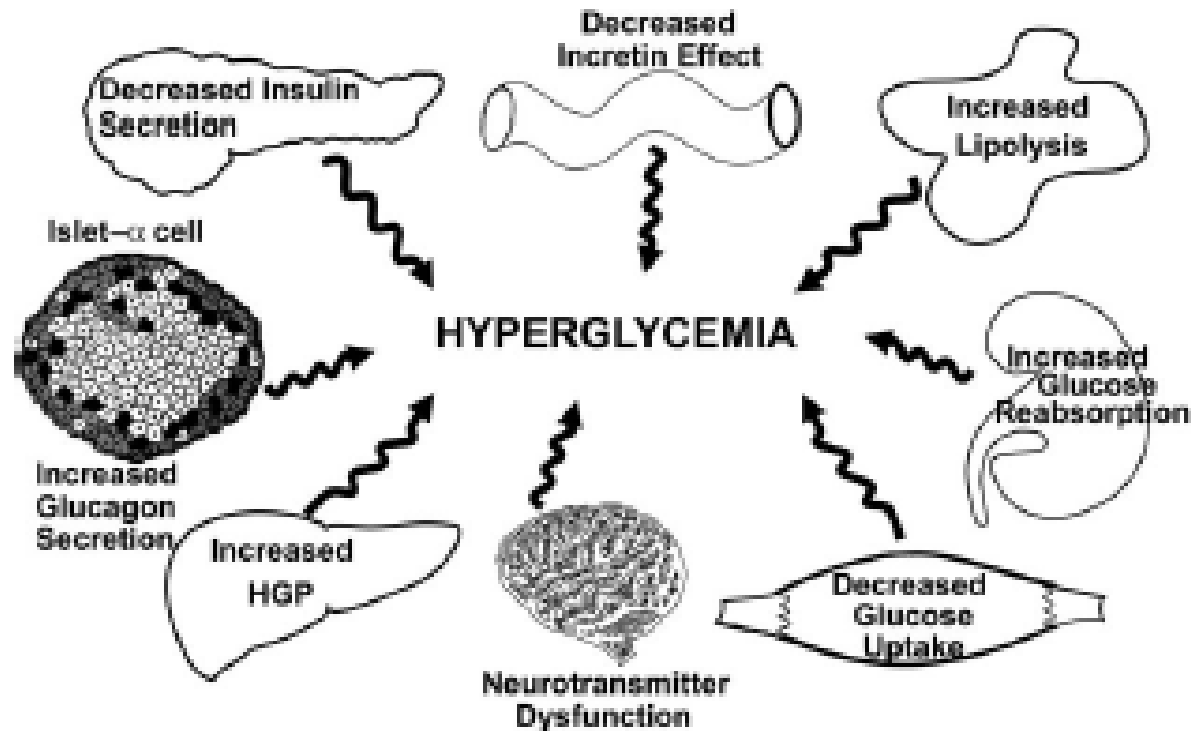
First was «the triumvirate».....



From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus

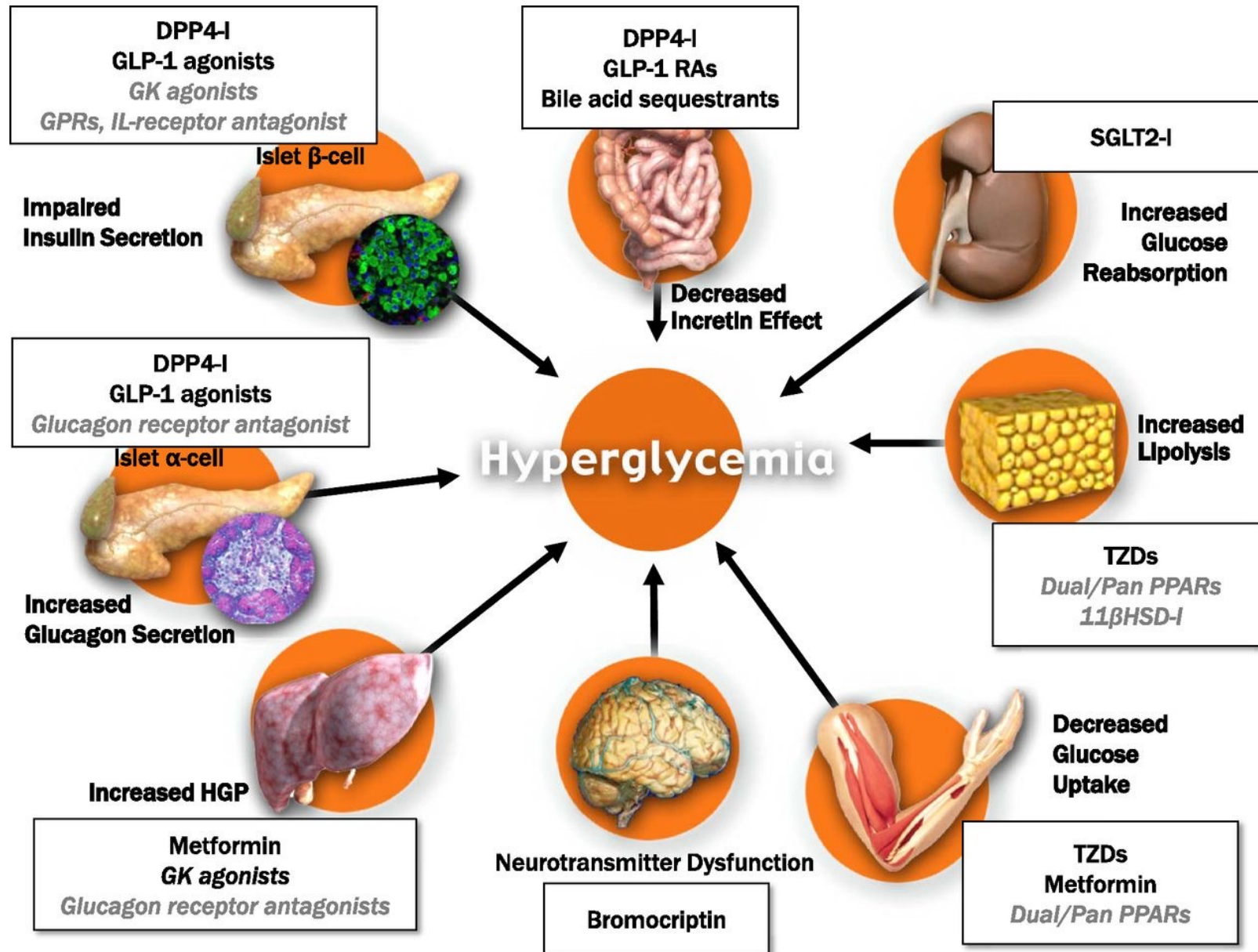
Ralph A. DeFronzo

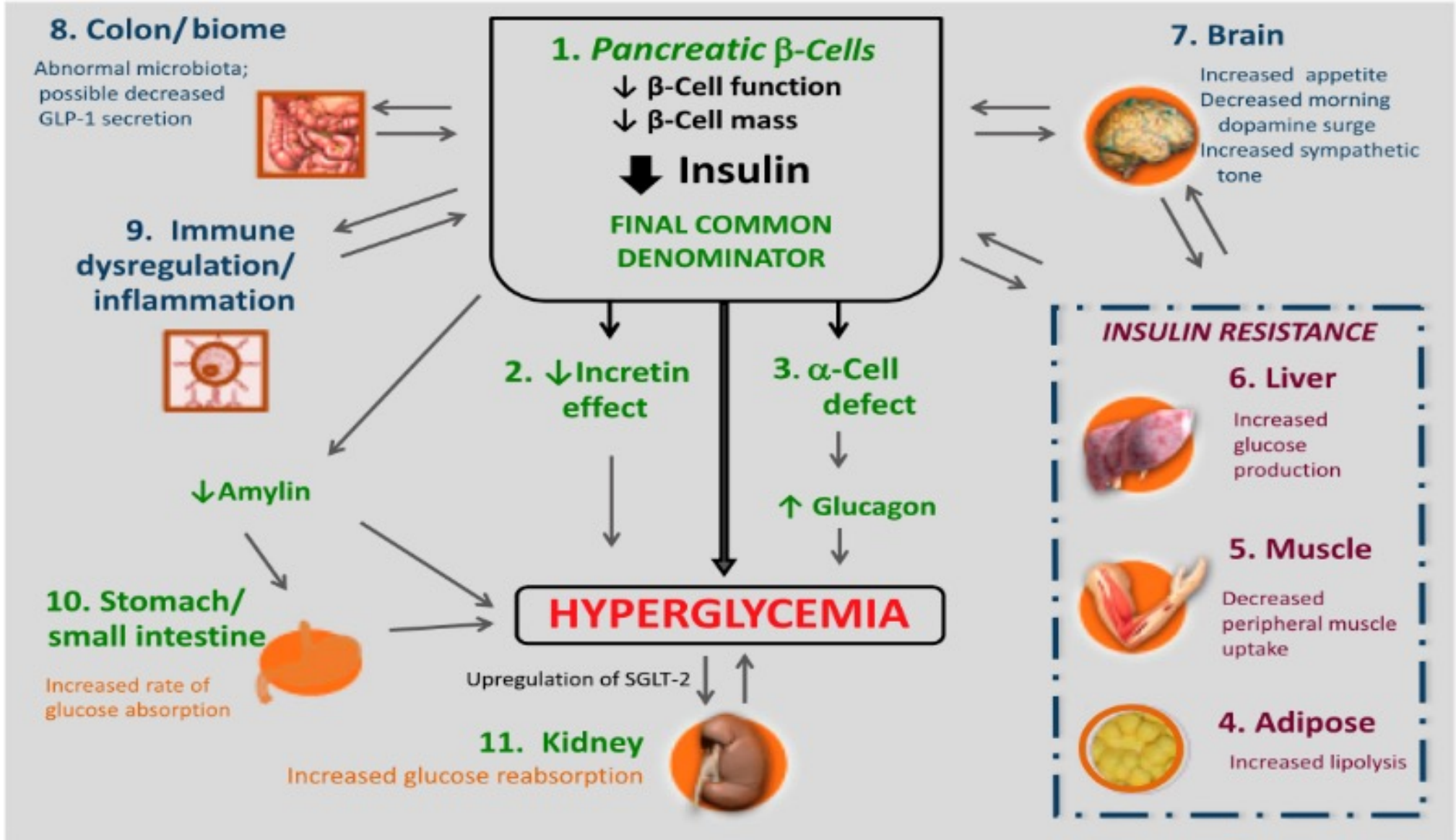
DIABETES, VOL. 58, APRIL 2009



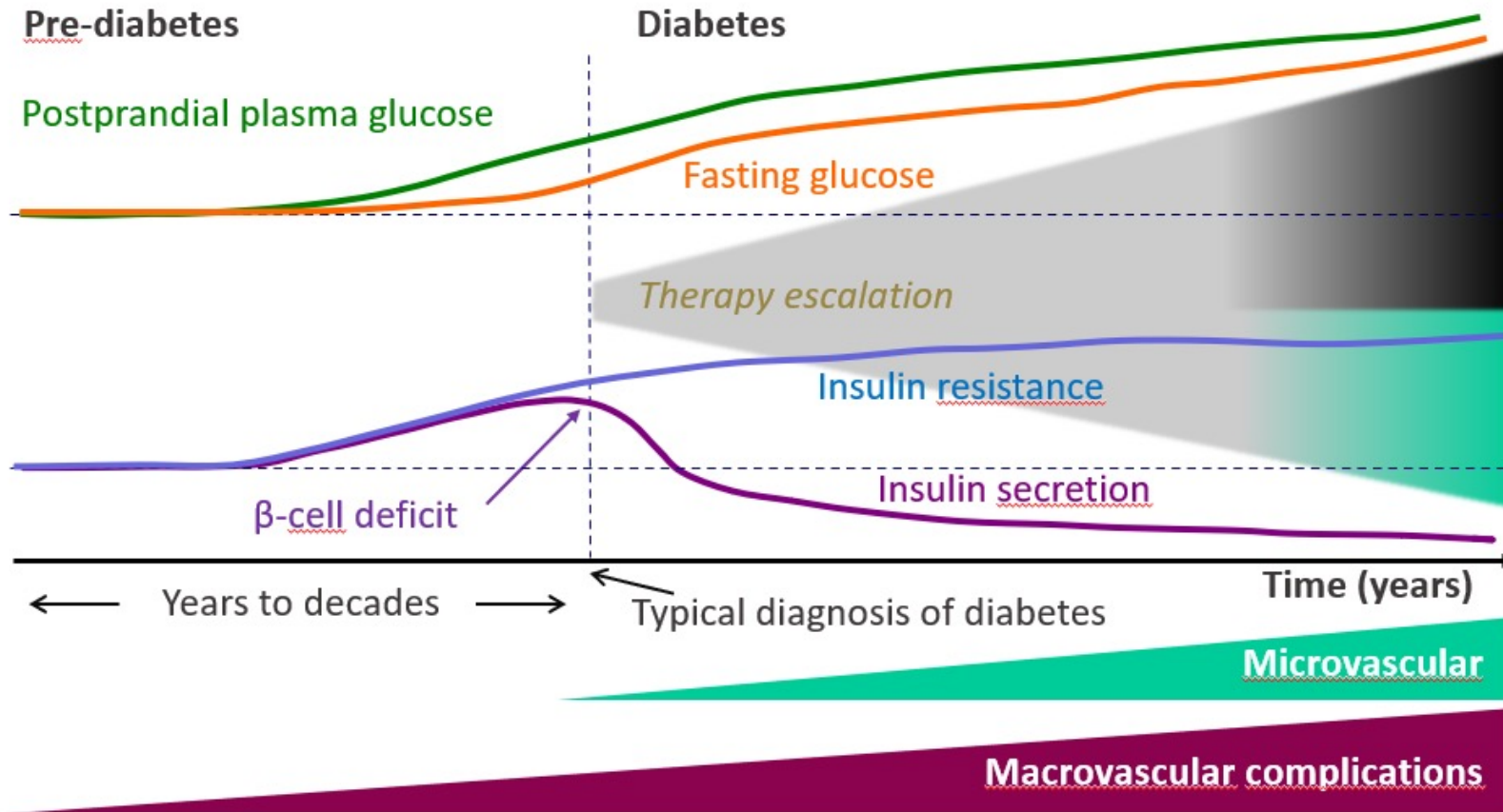
Pathogenesis of type 2 diabetes: implications for therapy

- 1) Effective treatment of type 2 diabetes requires multiple drugs used in combination to correct multiple pathophysiological defects.
 - 2) Treatment should be based on known pathogenic abnormalities and not simply on reduction of A1C.
 - 3) Therapy must be started early in the natural history of type 2 diabetes to prevent progressive β -cell failure.
-

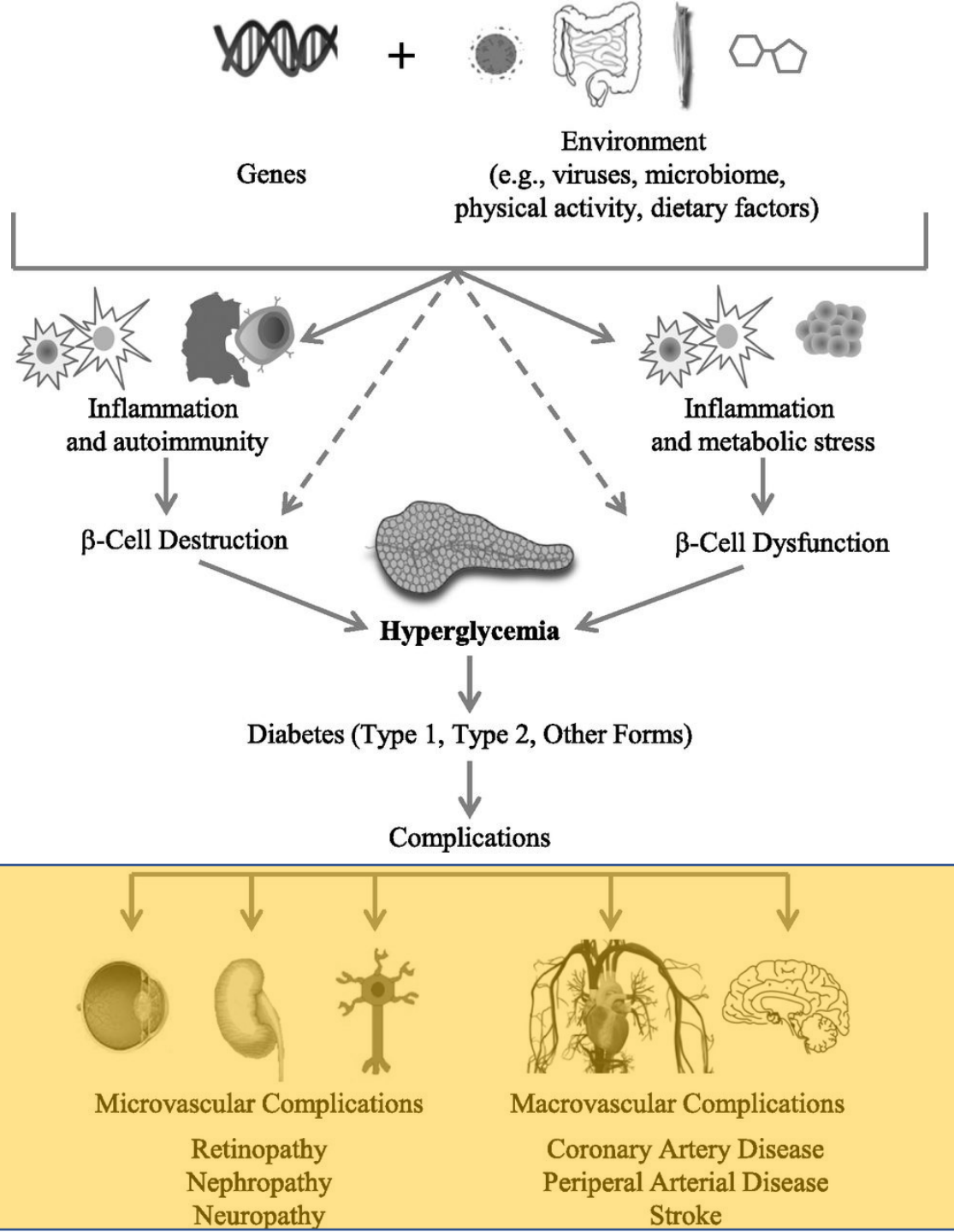




Storia naturale del diabete di tipo 2

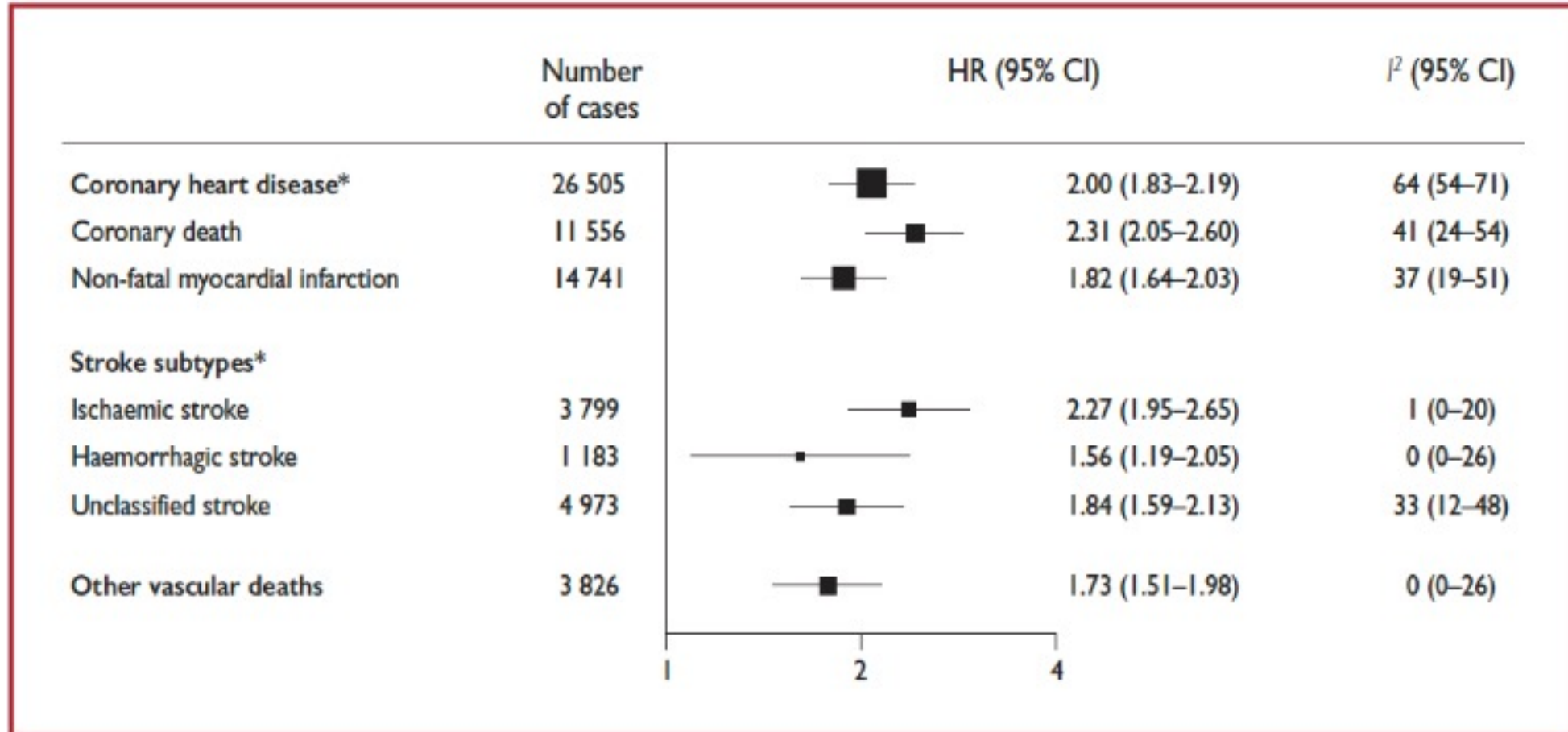


DIABETES MELLITUS – NATURAL HISTORY

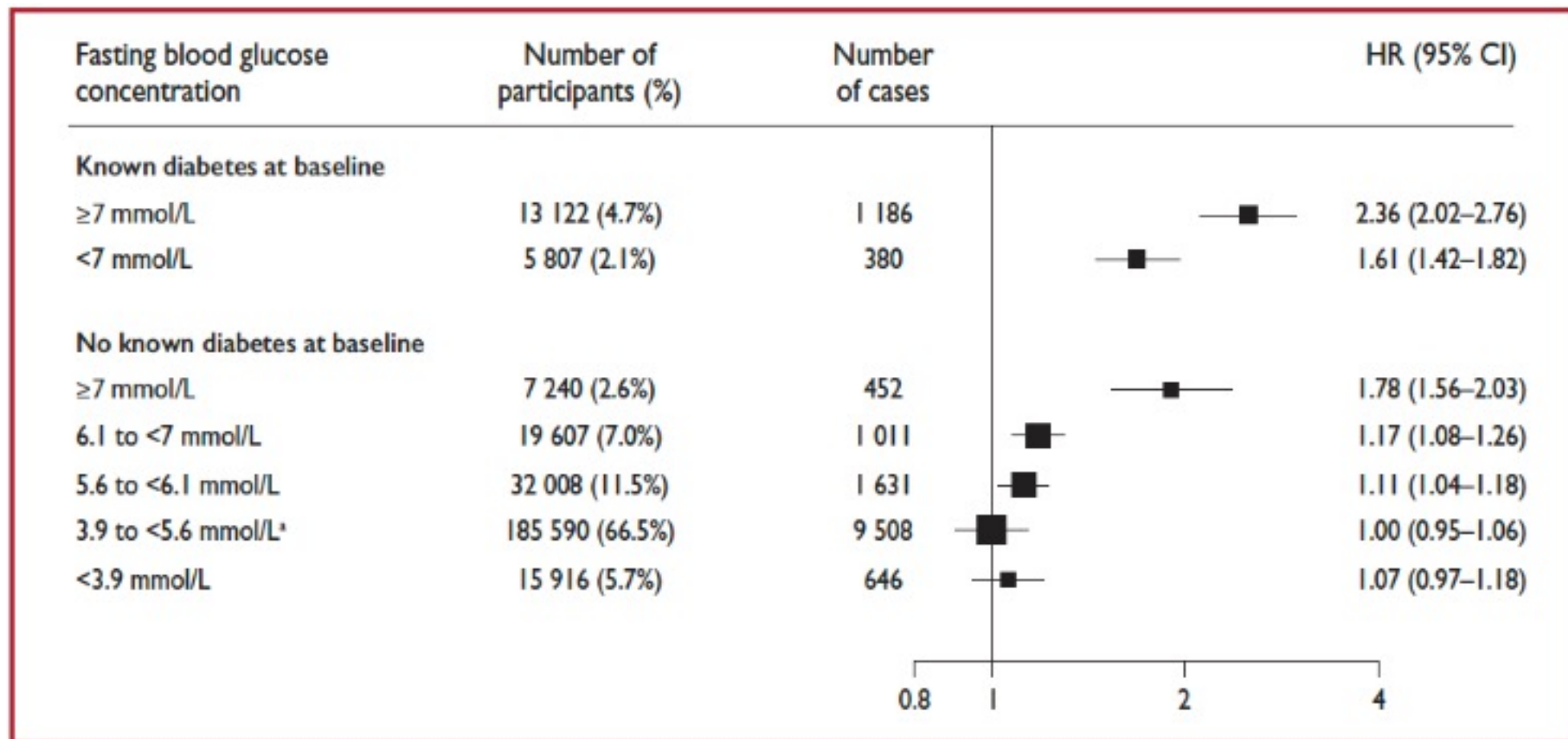


Skyler JS et al. Differentiation of Diabetes by Pathophysiology, Natural History, and Prognosis. Diabetes. 2017

Hazard ratios for vascular outcomes in people with vs. without diabetes mellitus at baseline, based on analyses of 530 083 patients



Hazard ratios for coronary heart disease by clinically defined categories of baseline fasting blood glucose concentration



Le 4 ere della cura del diabete

Era della sopravvivenza

Treat to survive

1922 Inizio
terapia
insulinica

Era del controllo dei sintomi

Treat to stay better

1955 Inizio
terapia con
farmaci orali

Era del buon controllo
glicemico per prevenire le
complicanze

Treat to target

1983
Risultati
DCCT

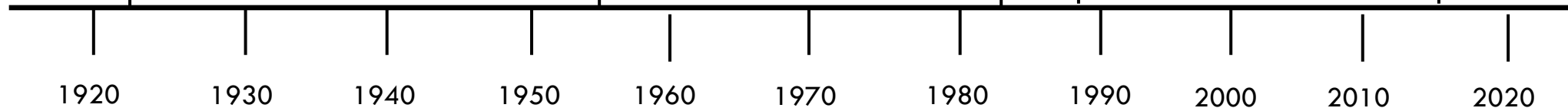
1988
Risultati
UKPDS

Era della prevenzione
cardiorenale

Treat to benefit

2015
Risultati
EMPA-
REG

2016
Risultati
LEADER



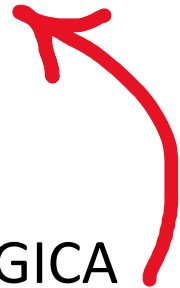
Adapted from Bonora E. presentation at «100 years of insulin»

APPROCCIO GLUCOCENTRICO

TRIALS DI INTERVENTO SUL CONTROLLO INTENSIVO DELLA GLICEMIA: UKPDS & DCCT

PRIMARY OUTCOME:

Il miglioramento del controllo glicemico riduce le complicanze micro e macrovascolari



DALL' ASSOCIAZIONE EPIDEMIOLOGICA

TRA

**IPERGLICEMIA E COMPLICANZE
MICROVASCOLARI**

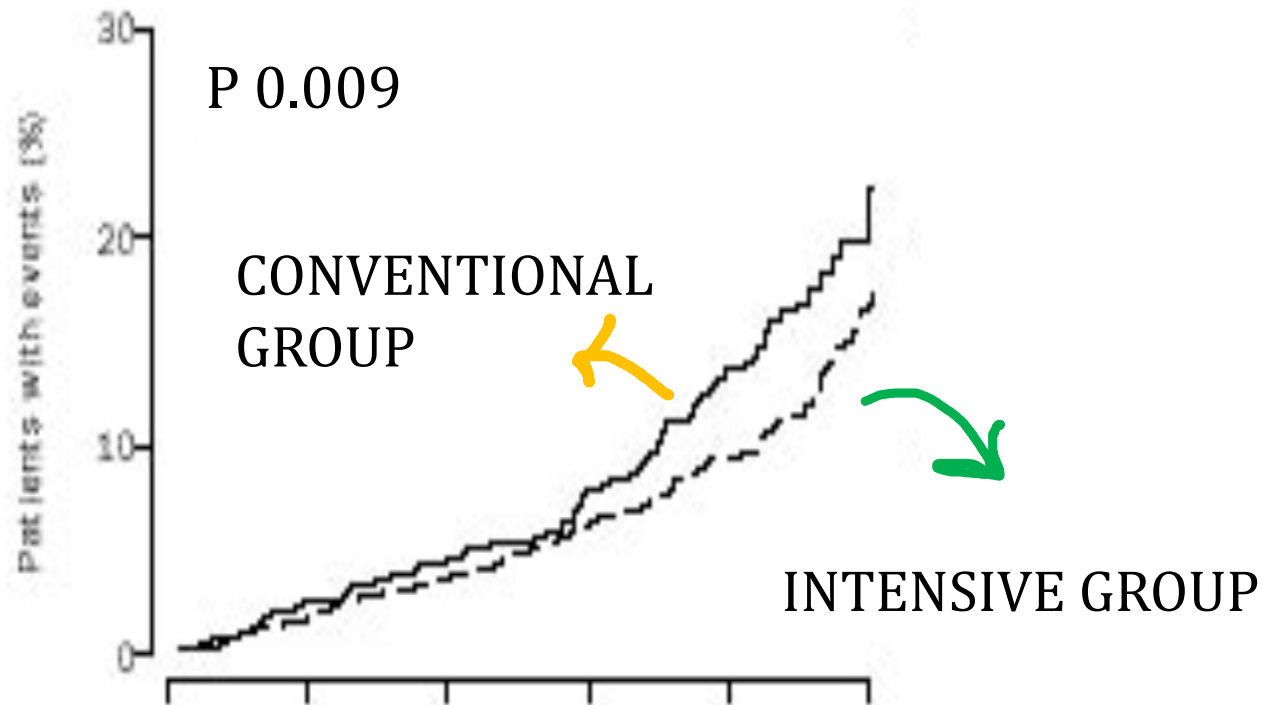


UKPDS- the lower, the better

GLYCEMIC TARGET IN CONVENTIONAL GROUP:
FPG < 270 MG/DL → DIET

GLYCEMIC TARGET IN INTENSIVE GROUP:
FPG < 108 MG/DL → INSULIN +/-SU +/- MET

MICROVASCULAR ENDPOINTS



NO SIGNIFICANCE REACHED FOR:

DIABETES-RELATED DEATHS
MACROVASCULAR ENDPOINTS
(P = 0,052)

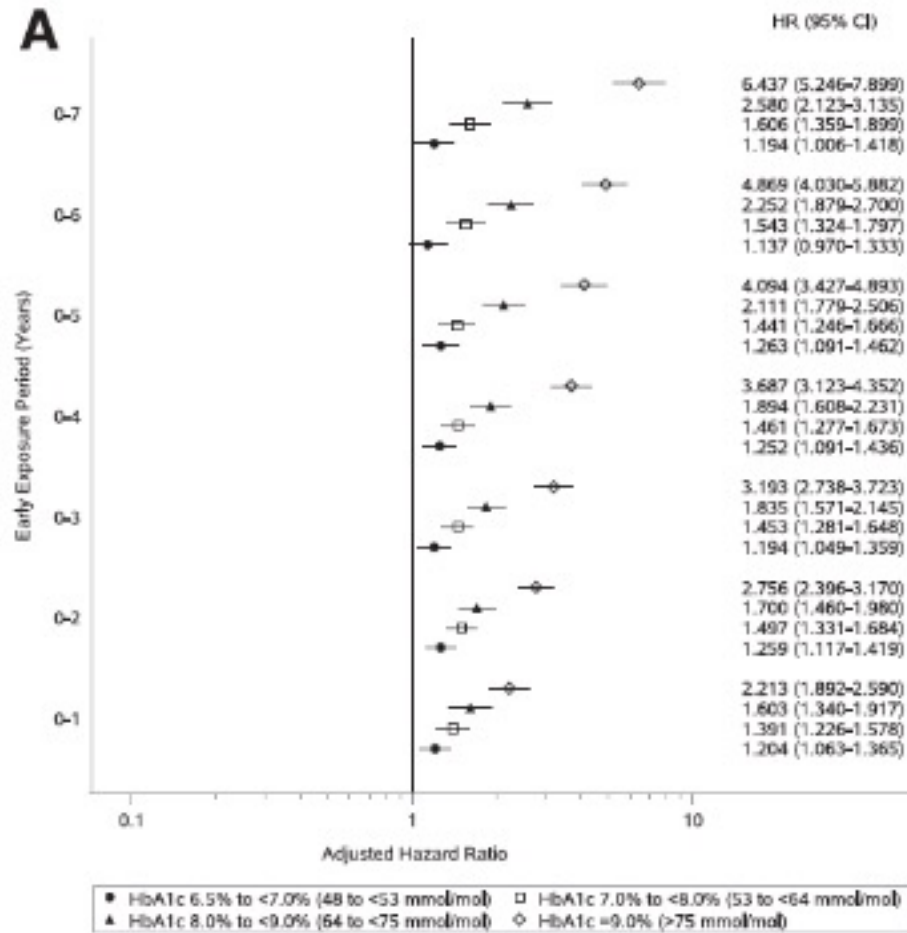
Legacy Effect of Earlier Glucose Control

After median 8.5 years post-trial follow-up

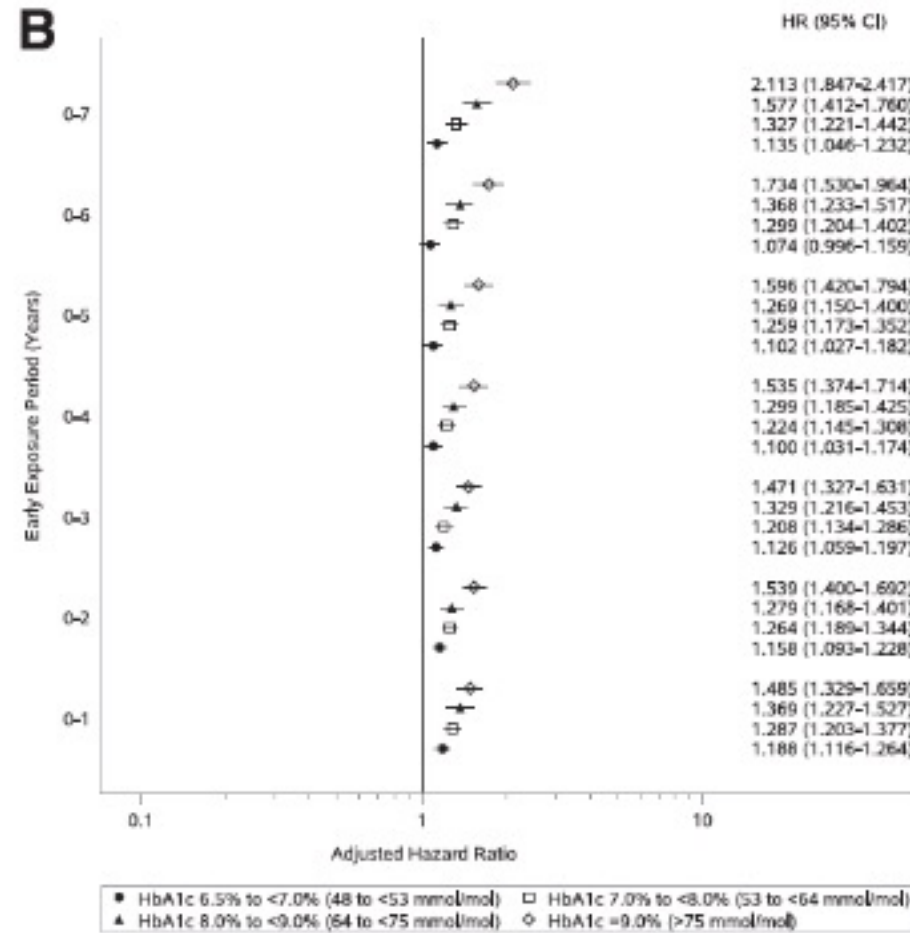
Aggregate Endpoint		1997	2007
Any diabetes related endpoint	<i>RRR:</i>	12%	9%
	<i>P:</i>	0.029	0.040
Microvascular disease	<i>RRR:</i>	25%	24%
	<i>P:</i>	0.0099	0.001
Myocardial infarction	<i>RRR:</i>	16%	15%
	<i>P:</i>	0.052	0.014
All-cause mortality	<i>RRR:</i>	6%	13%
	<i>P:</i>	0.44	0.007

RRR = Relative Risk Reduction, P = Log Rank

The Legacy Effect in Type 2 Diabetes: Impact of Early Glycemic Control on Future Complications



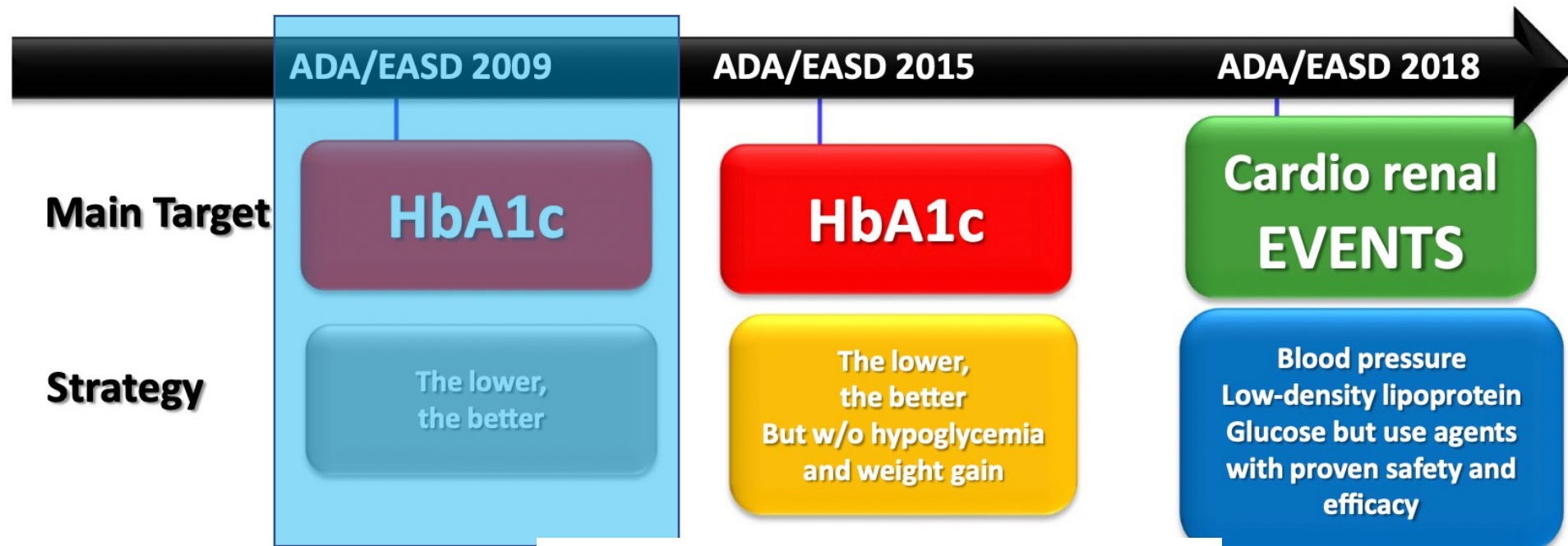
Microvascular events



Macrovascular events

EVOLUZIONE DELLE LINEE GUIDA

TREAT TO TARGET ERA



Recommendations

GLUCOSE-LOWERING DRUG EVALUATED IN RCTs:

ADA/ EASD 2018
ACC/AHA 2019
ESC/EASD 2019

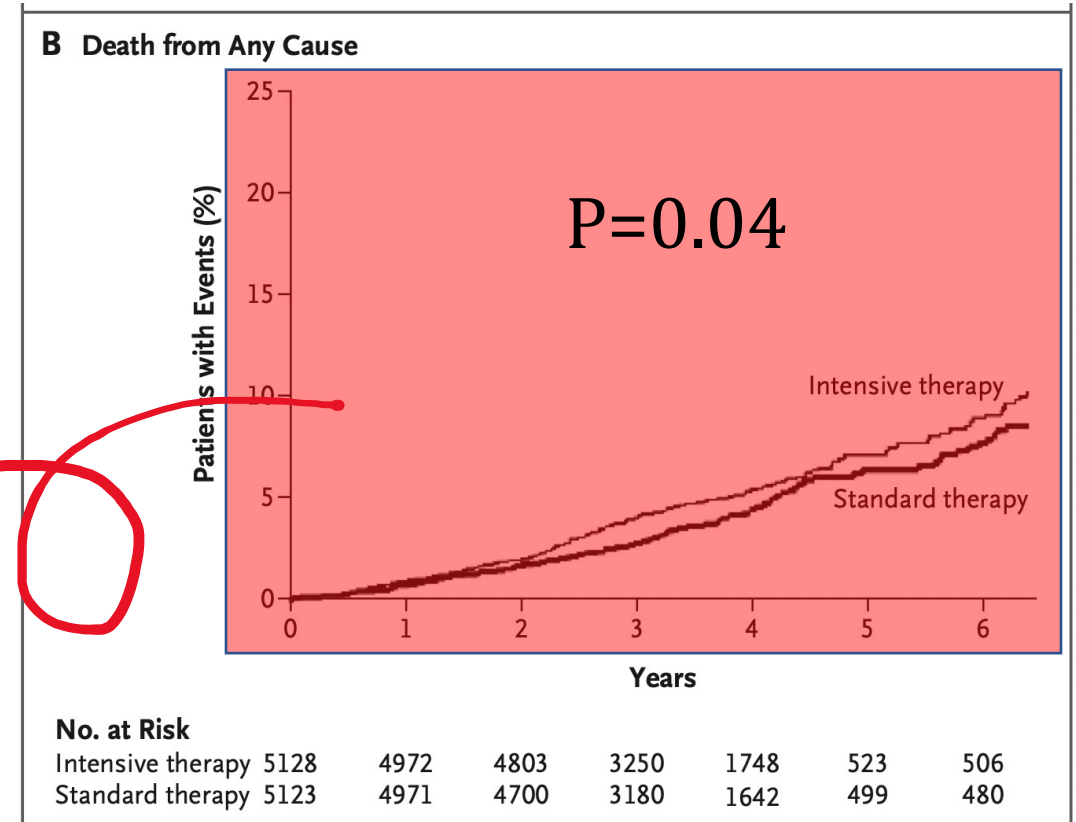
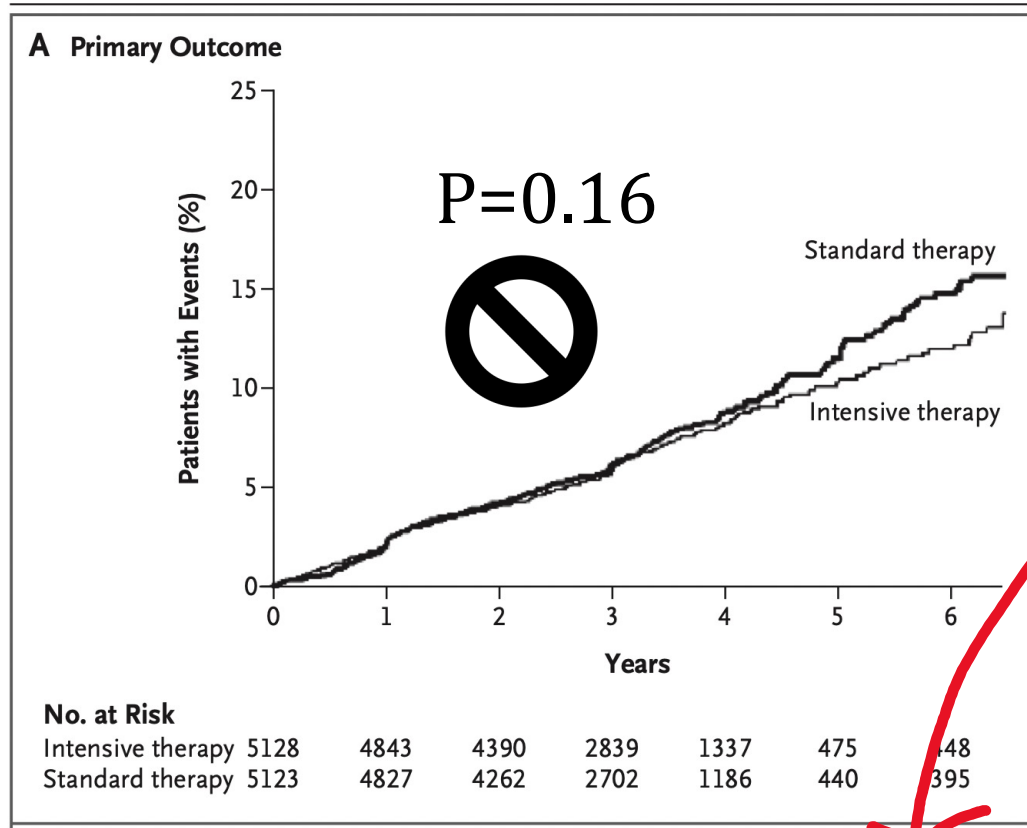
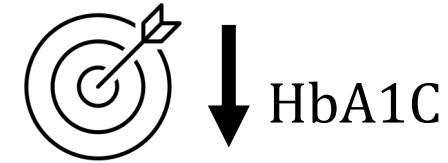


- INSULIN
- SULFONYLUREA
- BIGUANIDES

ACCORD- the lower, the better ???

GLYCEMIC TARGET IN CONVENTIONAL GROUP: $7 > \text{HbA1C} < 7.9\%$

GLYCEMIC TARGET IN INTENSIVE GROUP: **HbA1C < 6%**



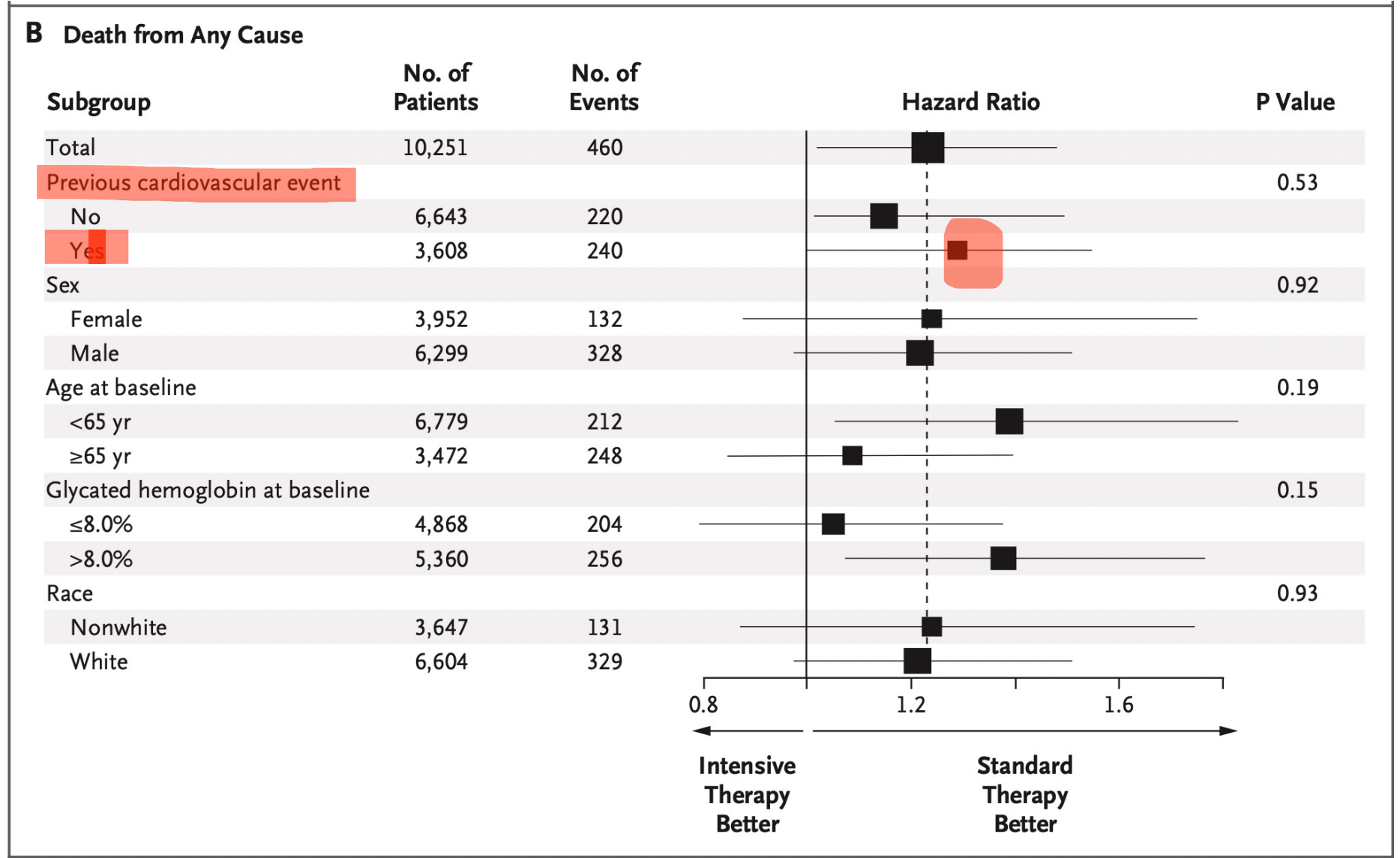
Hypoglycemia requiring assistance >> in the intensive-therapy group ($P < 0.001$)

ACCORD- the lower, the better ???



RISK >> BENEFIT

High-risk patients
with type 2 diabetes



Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials

Study	Micro-vascular		CVD		Mortality	
	Initial trial	Long-term follow-up	Initial trial	Long-term follow-up	Initial trial	Long-term follow-up
UKPDS ^[6,7]	↓	↓	↔	↓	↔	↓
DCCT ^[8] / EDIC ^{[9]*}	↓	↓	↔	↓	↔	↔
ACCORD ^[10]	↓		↔		↑	
ADVANCE ^[11]	↓		↔		↔	
VADT ^[12]	↓		↔		↔	

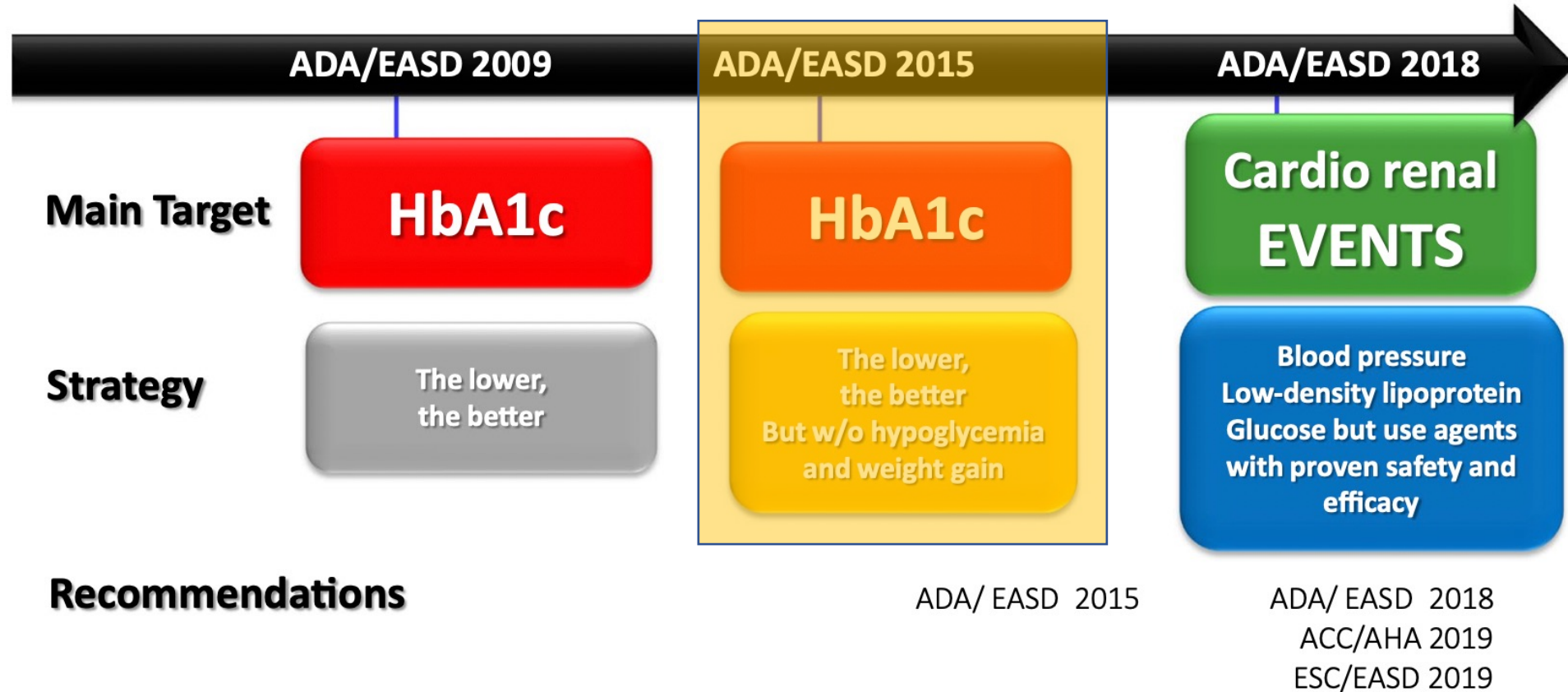
*in T1DM; CVD, cardiovascular disease.
For trial names and references, see text.

From Kendall DM, Bergenstal RM. © International Diabetes Center 2009.

Initial trial
Long-term follow-up

EVOLUZIONE DELLE LINEE GUIDA

TREAT TO TARGET (WITH CAUTION) ERA

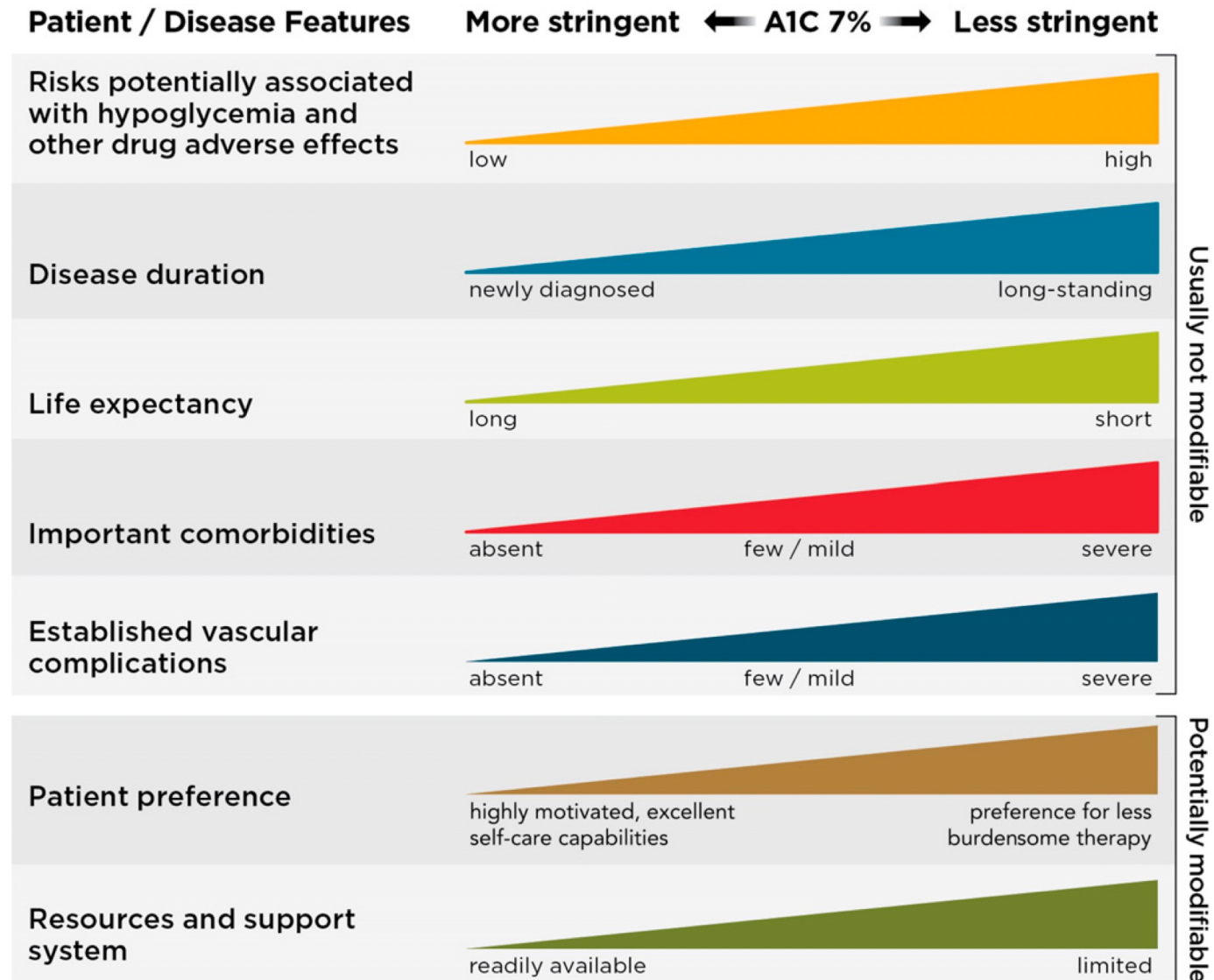


Lowering of HbA1c is not enough!!!

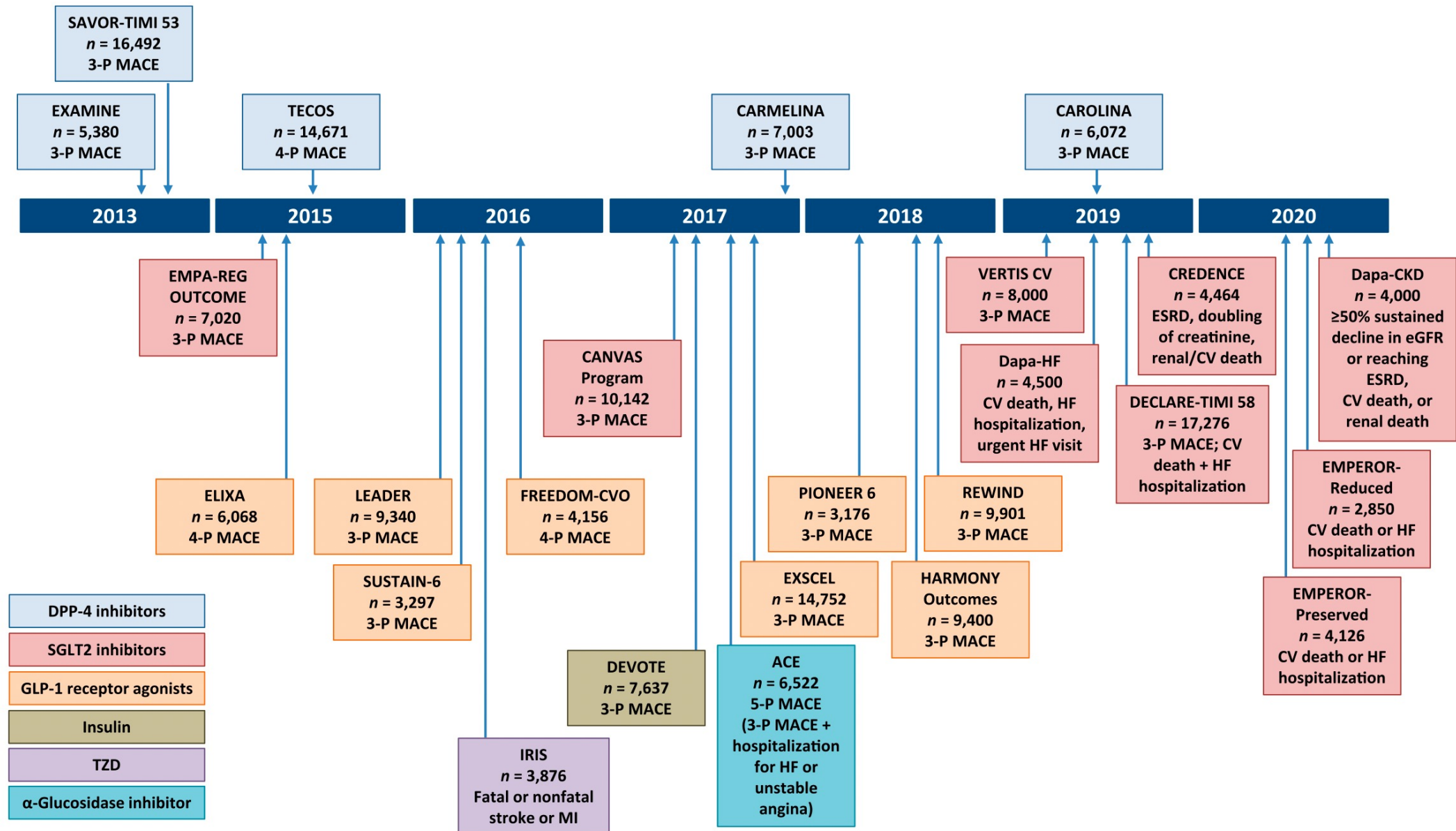


DRUG SAFETY

GOAL OF TREATMENT- the lower, the better BUT IN SAFETY

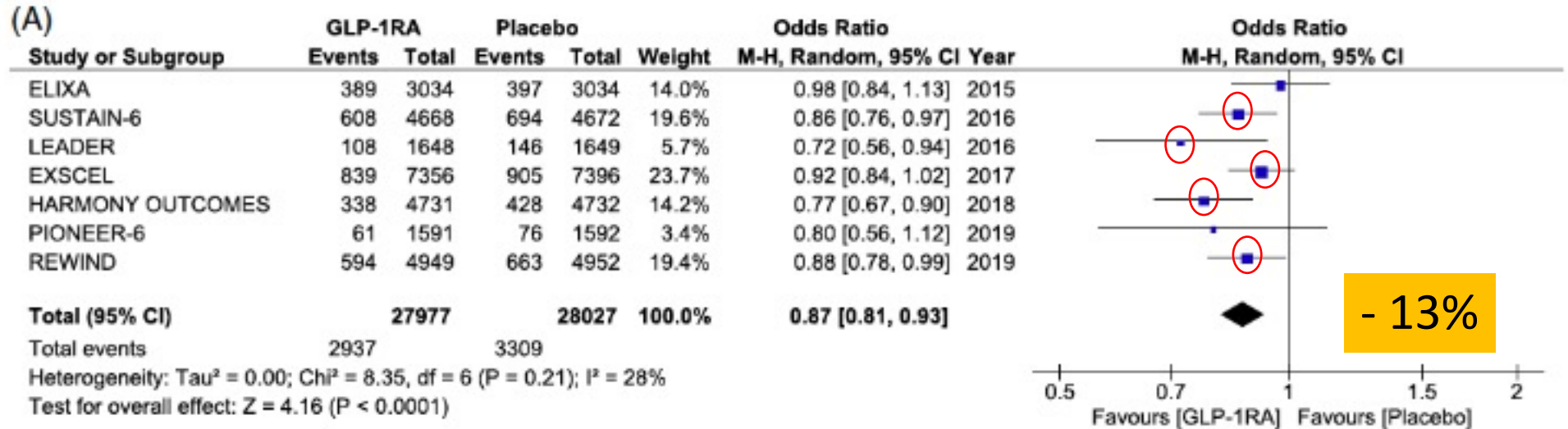


CARDIOVASCULAR OUTCOMES TRIALS IN TYPE 2 DIABETES

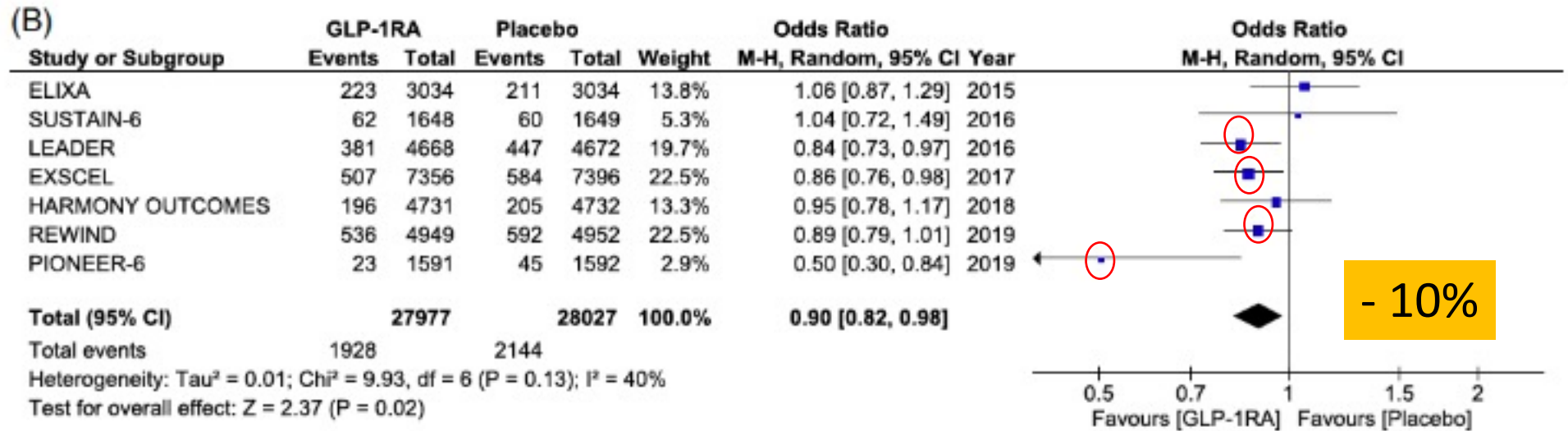


Cardioprotection of GLP-1RA

Risk of , major adverse cardiovascular events (MACE)



Risk of all cause mortality



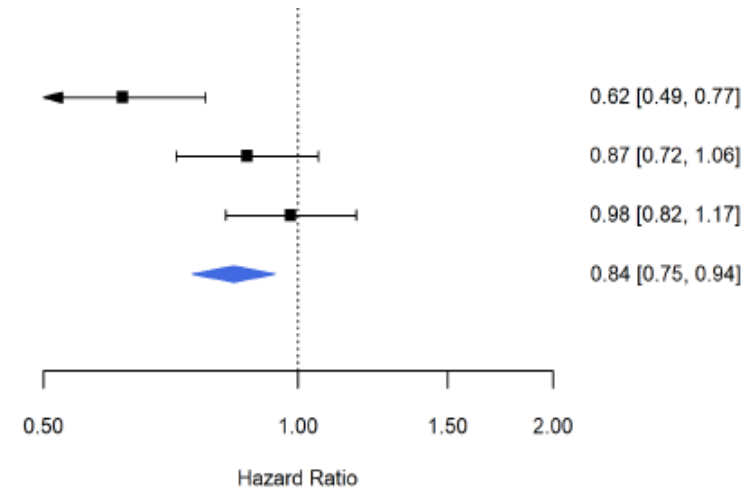
Cardioprotection of ISGLT-2

Risk of cardiovascular death

SGLT2i

EMPA-REG OUTCOME 7020	309	1.2	2.0	25.1
CANVAS Program	453	1.2	1.3	34.3
DECLARE-TIMI 58	494	0.7	0.7	40.6

Fixed Effects for CV Death (P-value=0.002)



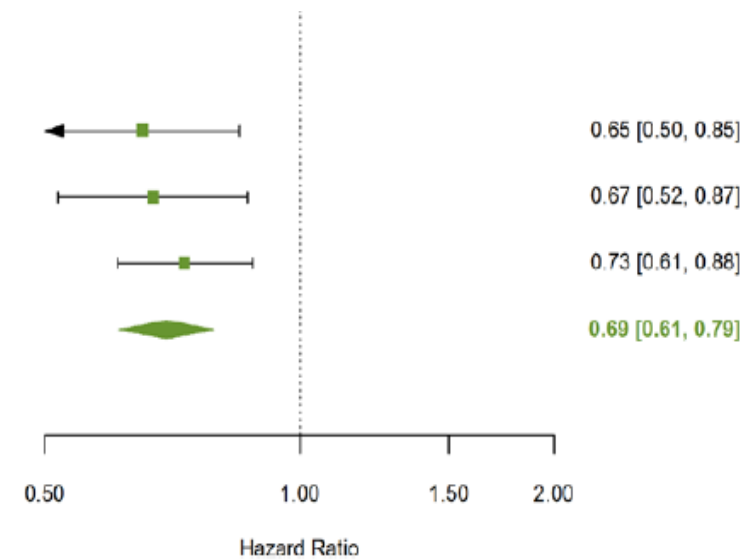
- 16%

Risk of HHF

SGLT2i

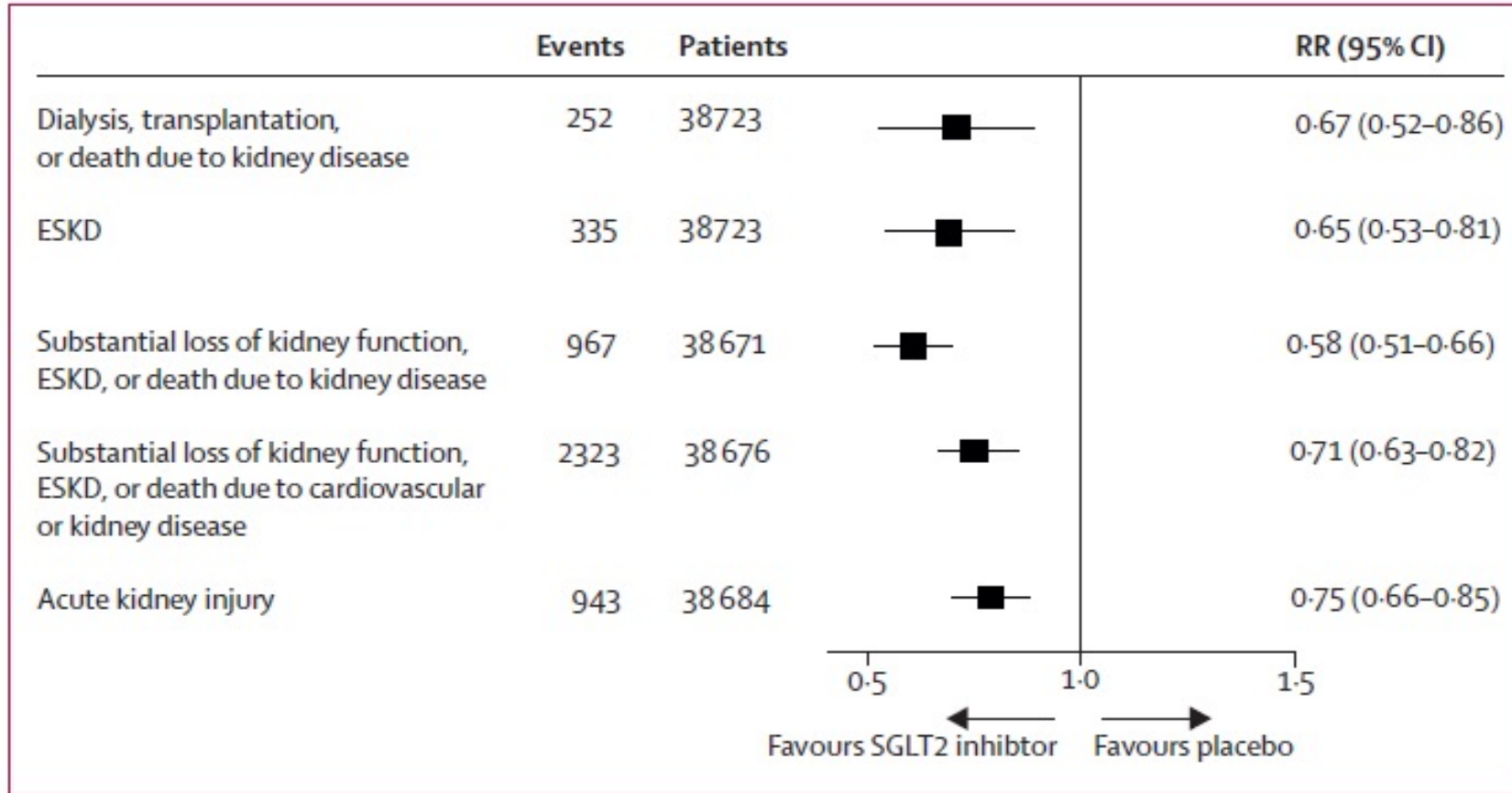
EMPA-REG OUTCOME 7020	221	0.9	1.4	24.0
CANVAS Program	243	0.6	0.9	25.6
DECLARE-TIMI 58	498	0.6	0.8	50.4

Fixed Effects for HHF (P-value<0.001)



- 31%

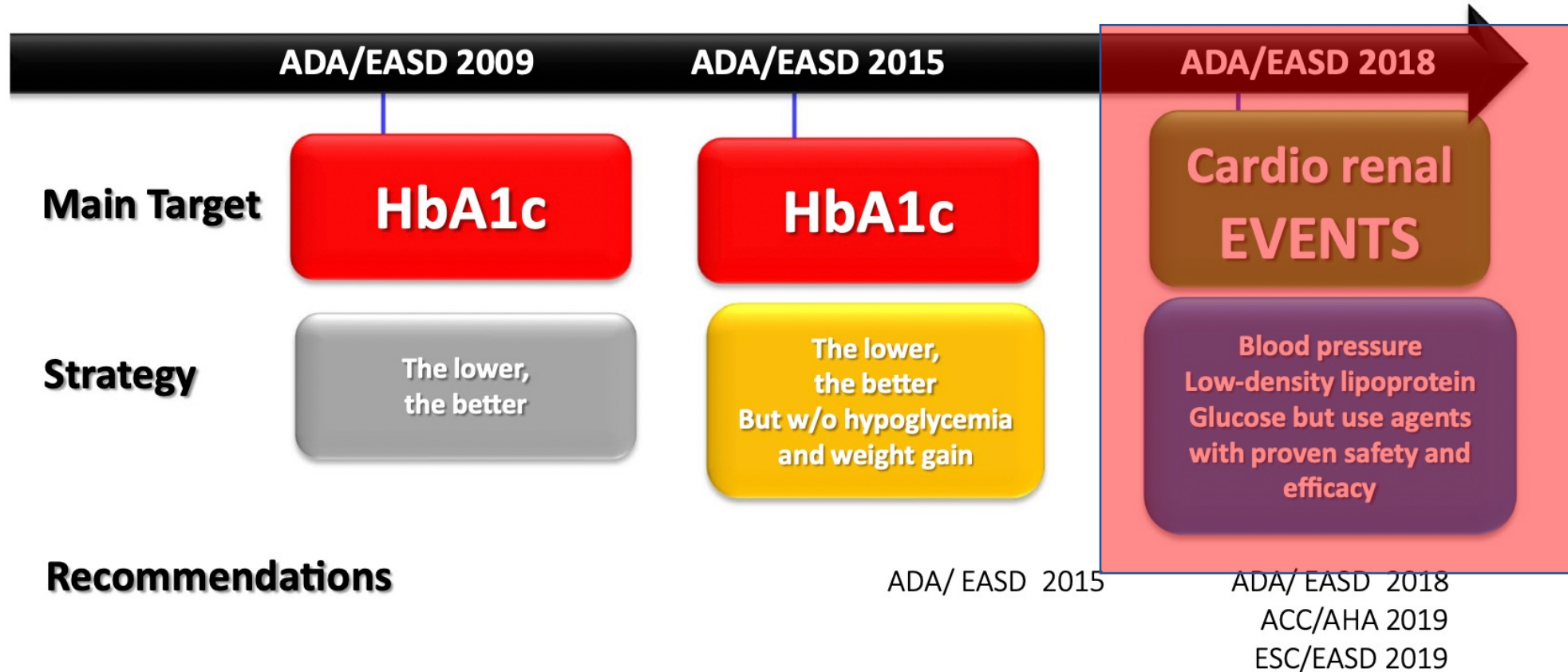
Renal protection of ISGLT-2



30 % ESKD
(renal death/dialysis/
renal transplantation)

EVOLUZIONE DELLE LINEE GUIDA

TREAT TO BENEFIT



SID/AMD 2021 – OBIETTIVI TERAPEUTICI



1.1 Si raccomanda un target di HbA1c tra 49 mmol/mol (6.6%) e 58 mmol/mol (7.5%) in pazienti con diabete di tipo 2 trattati con farmaci associati ad ipoglicemia.

Se rischio di ipoglicemia

$6,6 < \text{HbA1c} < 7,5\%$

1.2.1. Si raccomanda un target di HbA1c inferiore 53 mmol/mol (7%) in pazienti con diabete di tipo 2 trattati con farmaci non associati ad ipoglicemia.

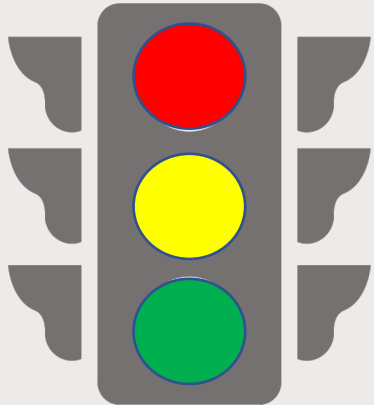
NO rischio ipoglicemia

$< 7\%$ è RACCOMANDATA

1.2.2. Si suggerisce un target di HbA1c inferiore o uguale a 48 mmol/mol (6.5%) in pazienti con diabete di tipo 2 trattati con farmaci non associati ad ipoglicemia.

NO rischio ipoglicemia

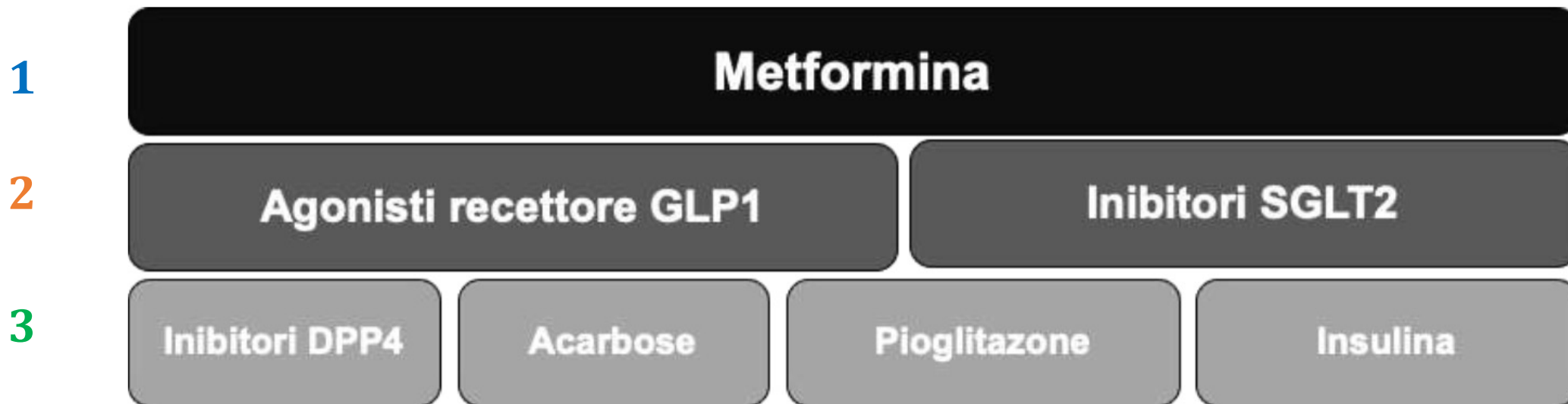
$< 6,5\%$ è SUGGERITA



SID/AMD 2021 – OBIETTIVI TERAPEUTICI



NO MALATTIA CARDIOVASCOLARE ACCERTATA



Le associazioni tra più farmaci devono essere prescritte secondo le indicazioni delle rispettive schede tecniche.



SU **non sono da considerare**
un'opzione terapeutica



Alto rischio di
ipoglicemia e di morte



MALATTIA ATEROSCLEROTICA ACCERTATA



Le associazioni tra più farmaci devono essere prescritte secondo le indicazioni delle rispettive schede tecniche.



5.2.1. Si raccomanda l'uso di metformina, SGLT-2i e GLP-1 RA come farmaci di prima scelta per il trattamento a lungo termine in pazienti con diabete di tipo 2 con pregressi eventi cardiovascolari e senza scompenso cardiaco. Pioglitazone, DPP-4i, acarbose ed insulina dovrebbero essere considerati farmaci di seconda scelta.

Forza della raccomandazione: forte. Qualità delle prove: moderata.



INSUFFICIENZA CARDIACA

1

Inibitori SGLT2

2

Agonisti recettore GLP1

Metformina*

3

Inibitori DPP4**

Acarbose

Insulina

Le associazioni tra più farmaci devono essere prescritte secondo le indicazioni delle rispettive schede tecniche.

** La metformina è controindicata in classe III e IV NYHA; ** Saxagliptin è associato ad un aumento di ricoveri per scompenso cardiaco*

5.2.2. Si raccomanda l'uso di SGLT-2i come farmaci di prima scelta per il trattamento a lungo termine di pazienti con diabete di tipo 2 con scompenso cardiaco. I GLP-1 RA e metformina dovrebbero essere considerati come farmaci di seconda scelta, mentre DPP-4i, acarbose ed insulina come farmaci di terza scelta.

Forza della raccomandazione: forte. Qualità delle prove: moderata.

TAKE HOME MESSAGES

- Nell'era del «treat to benefit» la terapia del diabete deve tener conto delle potenzialità dei farmaci oggi disponibili (GLP-1 analoghi, ISGLT2)
- Le attuali linee guida, sulla scorta di una rigorosa revisione della letteratura scientifica, certificano la necessità di trattare i pazienti diabetici con malattia cardiovascolare, scompenso cardiaco, nefropatia con farmaci antidiabetici di provata efficacia su tali condizioni
- Non si deve dimenticare l'importanza del controllo glicemico (con target personalizzati)