Prevenzione cardiovascolare nel paziente diabetico: target metabolici e importanza del trattamento insulinico tempestivo

Alberto Aglialoro
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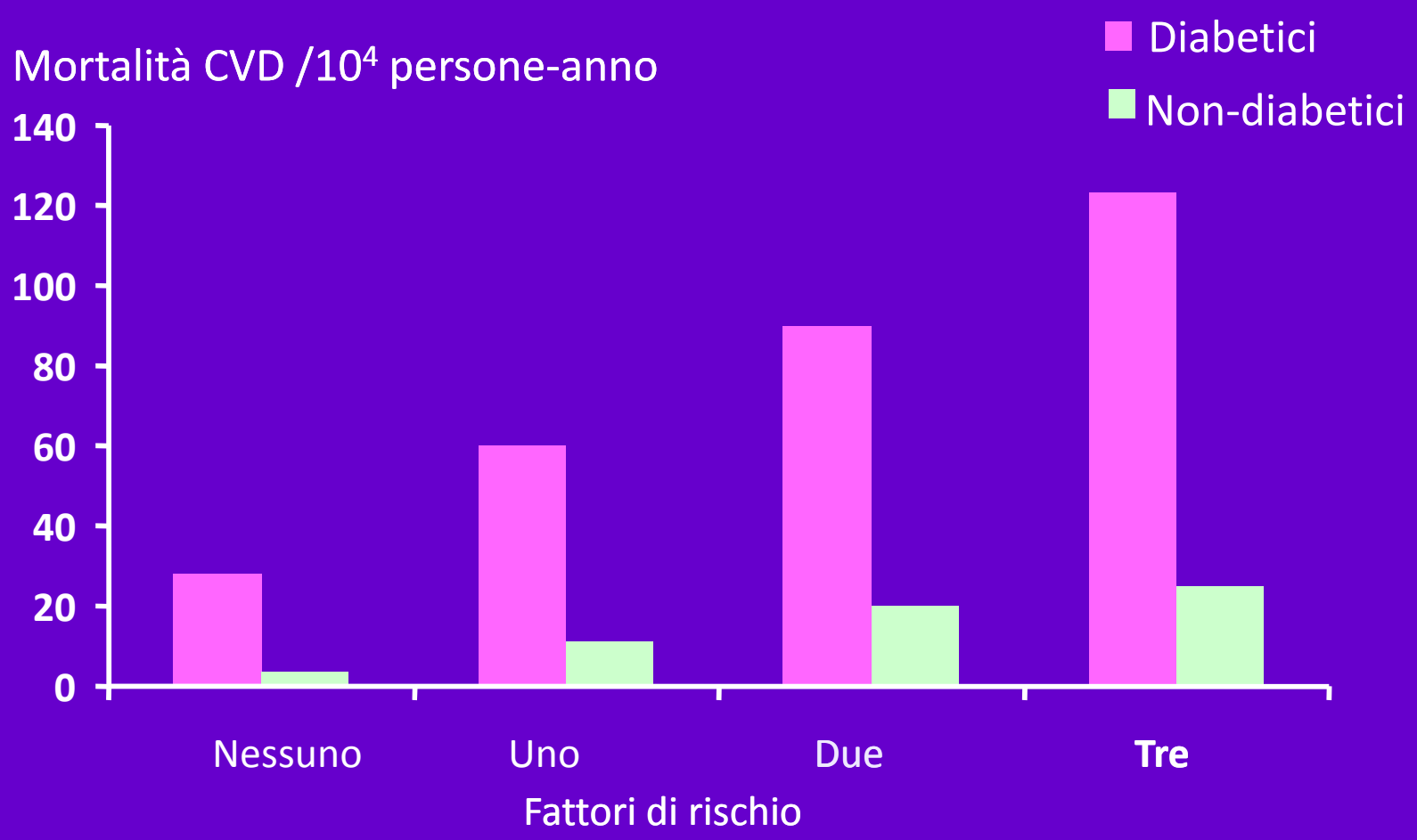
“ DIABETES IS A CARDIOVASCULAR DISEASE DIAGNOSED BY MEASURING GLYCAEMIA”

Klas Malmberg -2001

LA MALATTIA CARDIOVASCOLARE NEL DIABETE TIPO 2

- E’ la più importante causa di morbidità e mortalità
- Il rischio di IMA aumenta da 3 a 5 volte
- La sopravvivenza dopo IMA, CABG e PTCA è ridotta
- Il rischio di stroke aumenta da 2 a 3 volte
- Il rischio di amputazioni aumenta di 10-15 volte

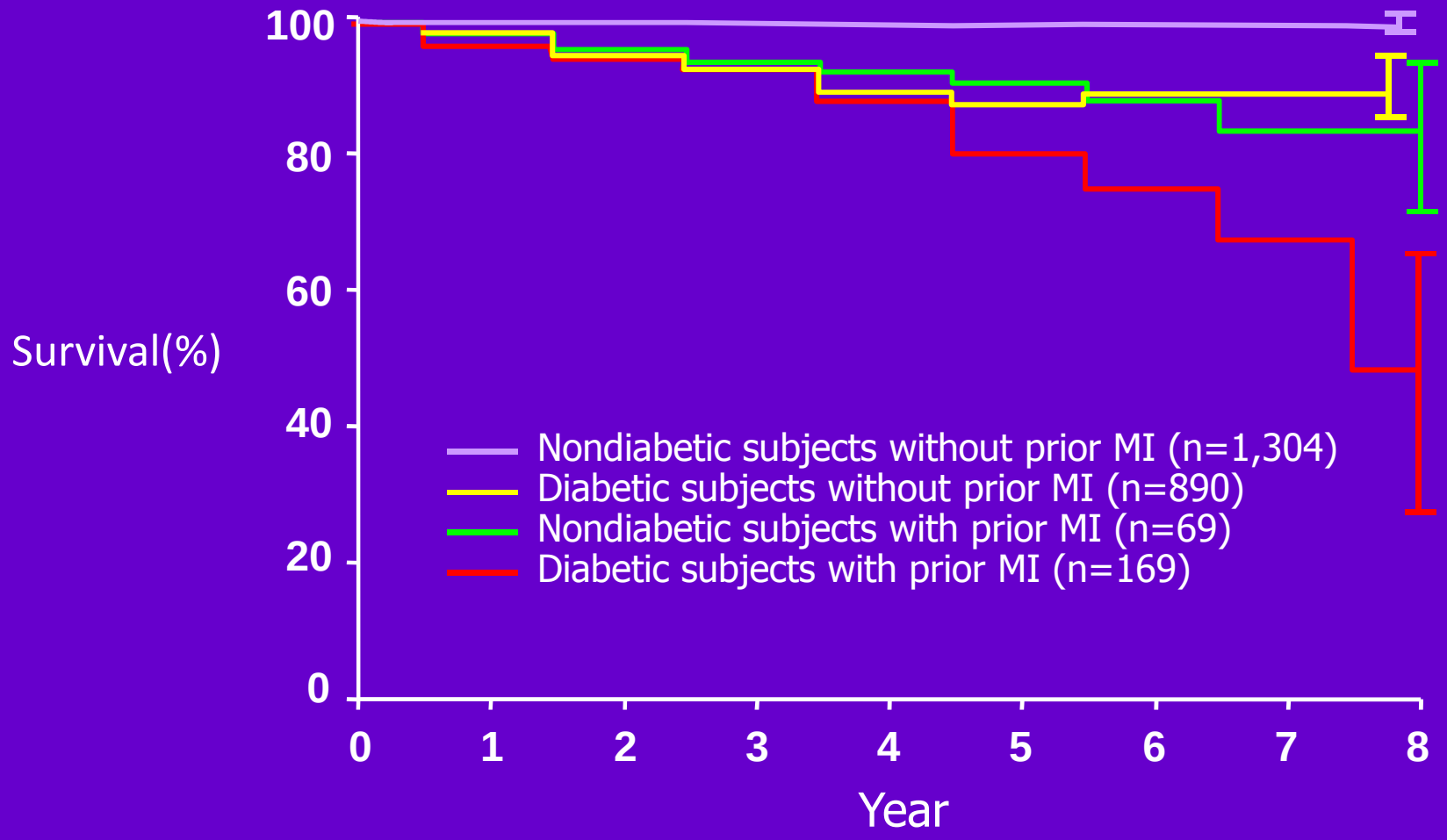
Mortalità cardiovascolare e diabete



Ipercolesterolemia, ipertensione arteriosa,fumo di sigarette

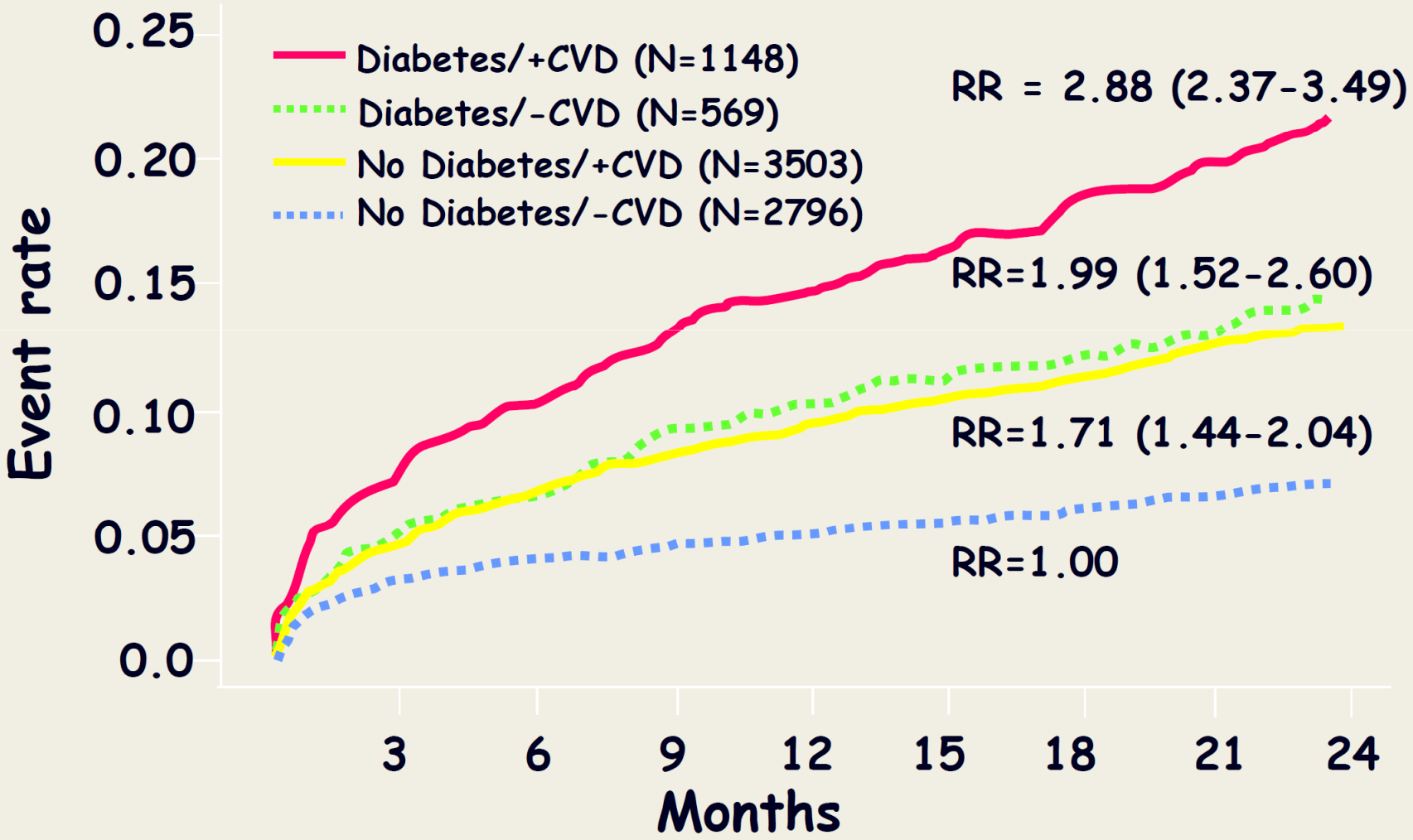
MRFIT Multiple Risk Factor Intervention Trial, Stamler et al (1993)

Similitudine di rischio tra diabetici (tipo 2) senza precedente IMA verso non diabetici (tipo 2) con precedente IMA



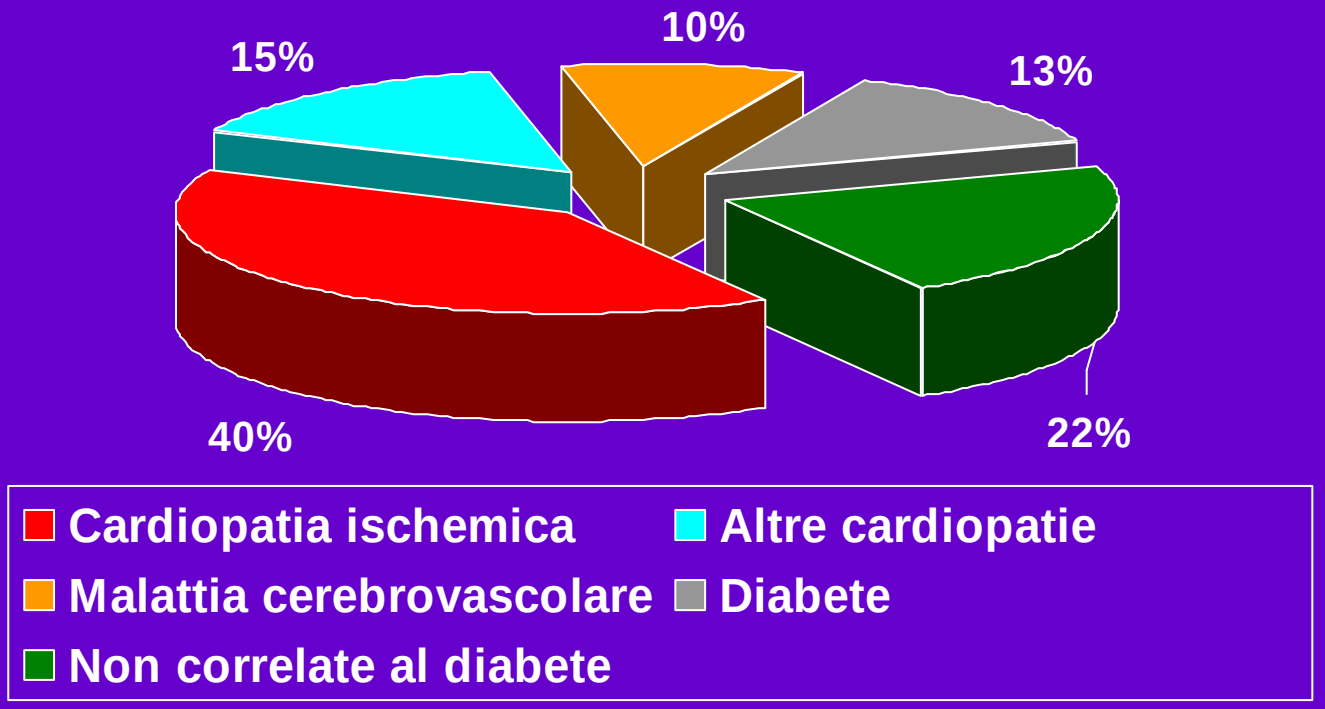
Haffner SM et al. *N Engl J Med.* 1998;339:229-234

Studio OASIS: Mortalità totale

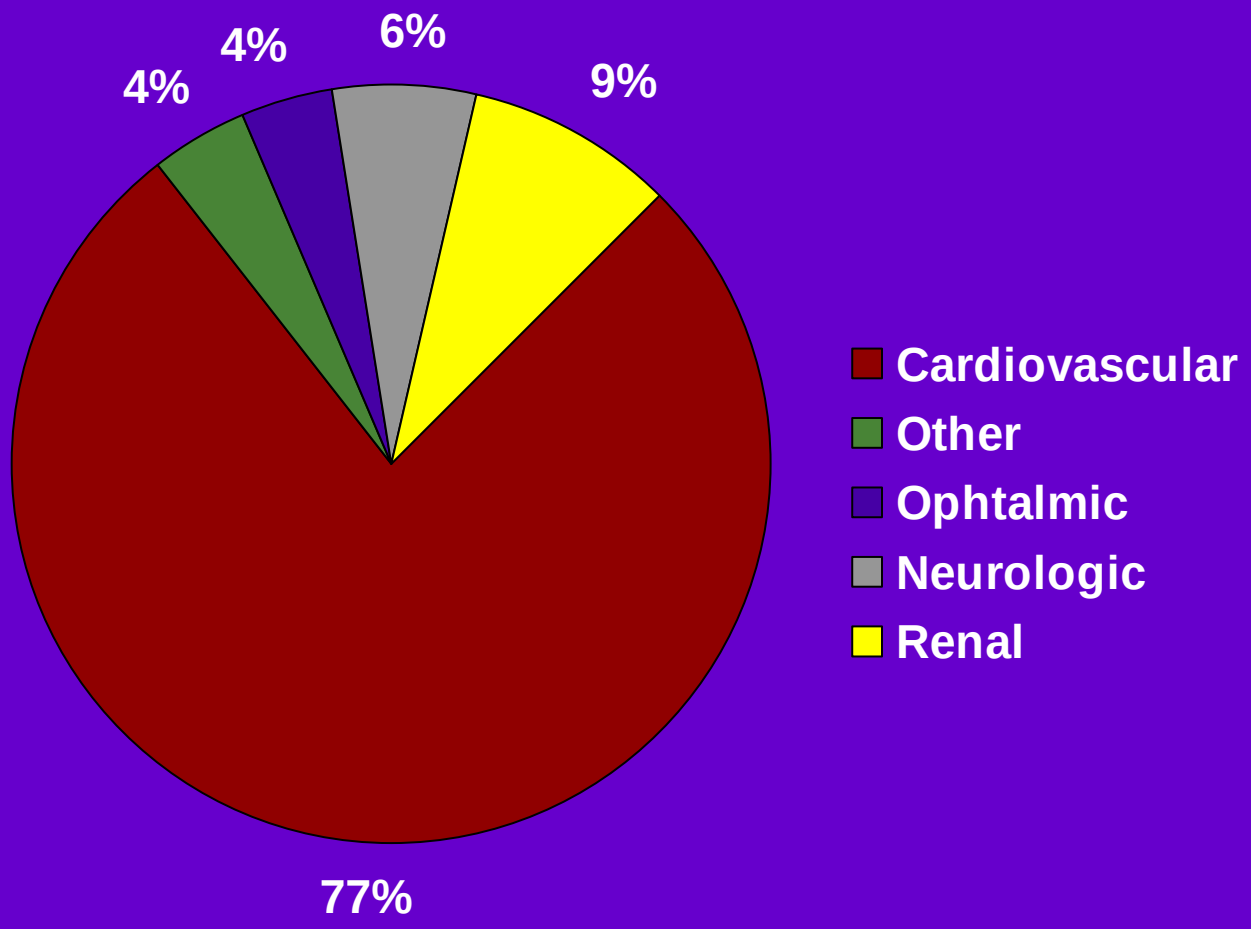


K Malmberg, et al. Circulation 102:1014-1019, 2000

Cause di morte nel diabete tipo 2 di lunga durata (Diabetes Vital Statistics, ADA 2001)



CAUSE DI OSPEDALIZZAZIONE



ADA, 1989

Il concetto di Diabete e malattia cardiovascolare si è evoluto da fattore di rischio di patologia cardiovascolare ad equivalente di patologia cardiovascolare

Goals of Therapy in Type 2 Diabetes

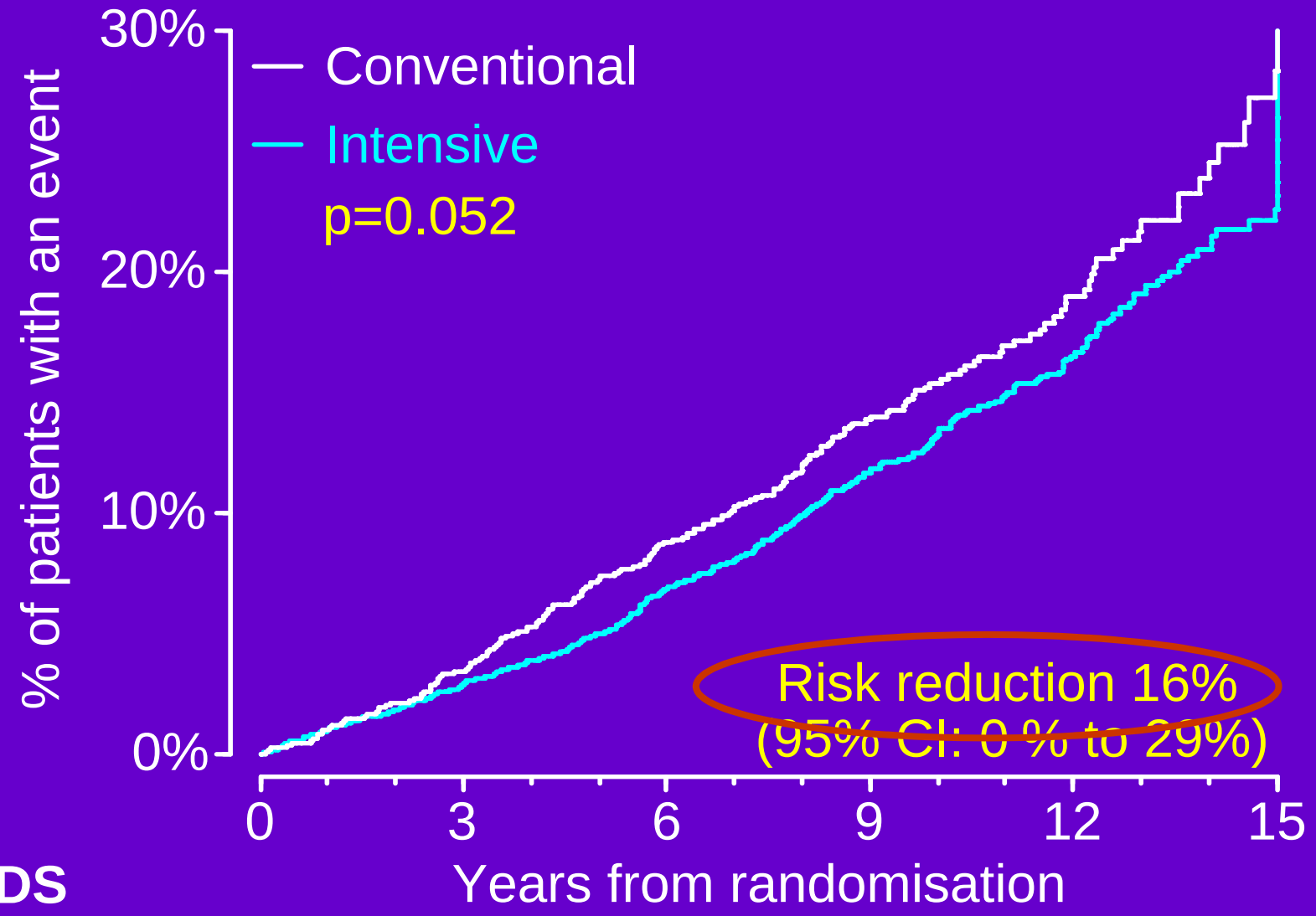
- To reduce the excess of cardiovascular disease
- To lower the incidence of microvascular disease
- To improve the quality of life
- To meet patient's compliance (administration of drugs, hypoglycemia)

Glycemic control and CVD

the Lower is the Better ?

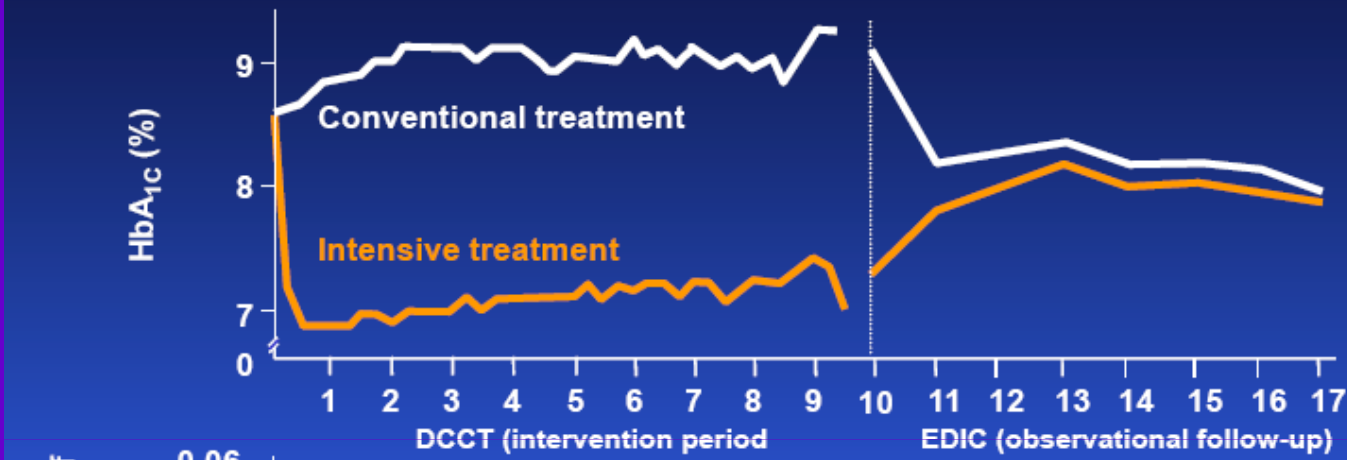
Myocardial Infarction (cumulative)

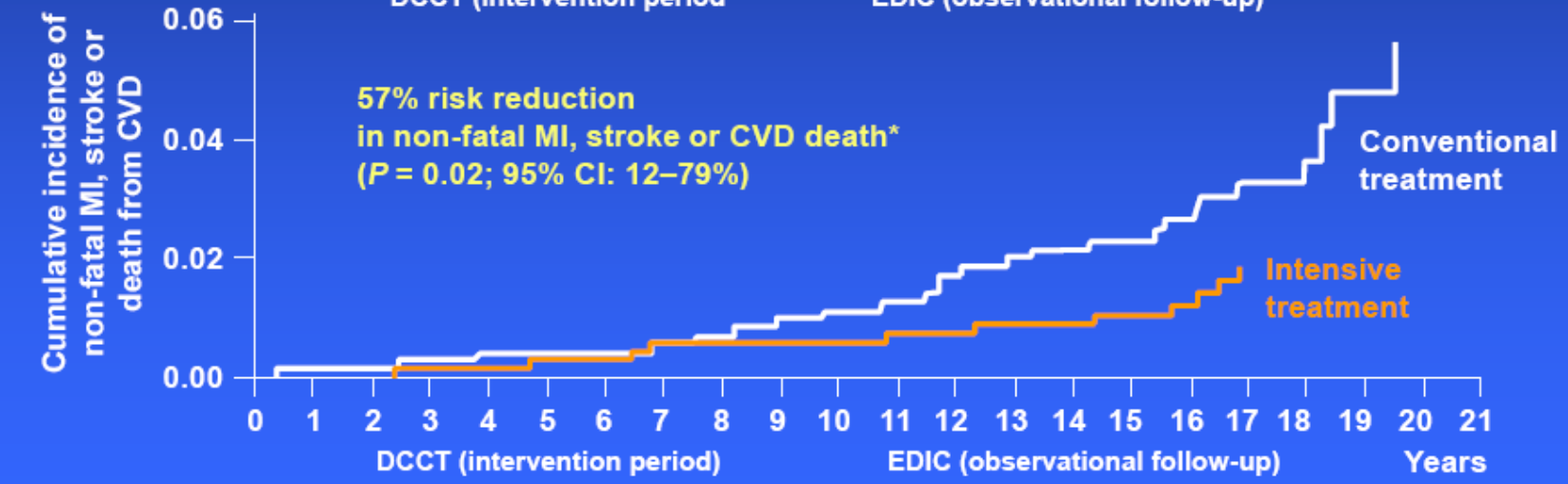
fatal or non fatal myocardial infarction, sudden death
573 of 3867 patients (15%)



UKPDS

DCCT/EDIC: glycaemic control reduces the risk of non-fatal MI, stroke or death from CVD in type 1 diabetes



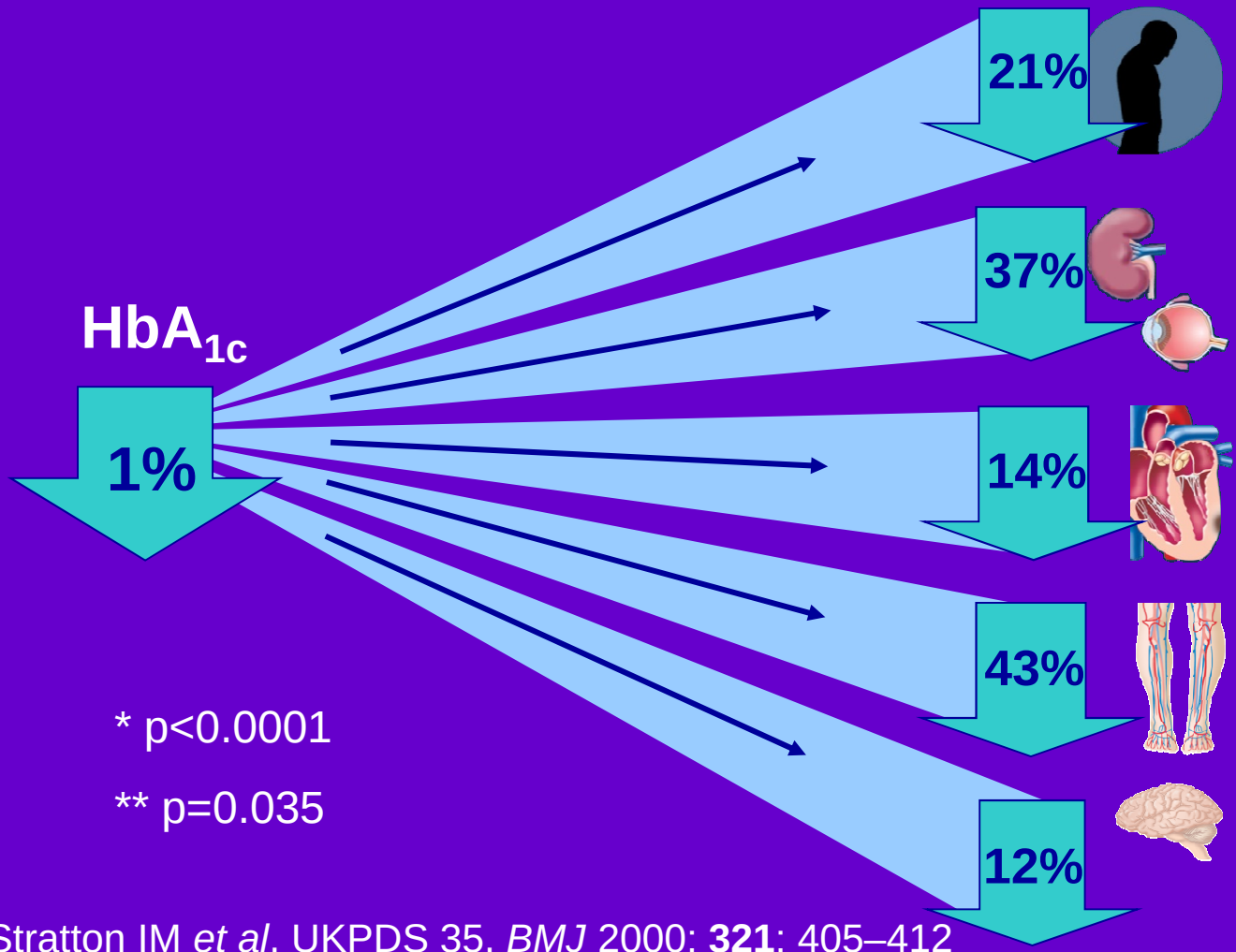


*Intensive vs conventional treatment

Adapted from DCCT. *N Engl J Med* 1993; 329:977–986. DCCT/EDIC. *JAMA* 2002; 287:2563–2569. DCCT/EDIC. *N Engl J Med* 2005; 353:2643–2653.

UKPDS: Tight Glycaemic Control Reduces Complications

Epidemiological extrapolation showing benefit of a 1% reduction in mean HbA_{1c}



* p<0.0001

** p=0.035

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

Translating clinical trials

Into

Clinical Practice

ACCORD

ADVANCE

VADT

?

STENO-2

?

ADOPT

UKPDS

?

Lot's RCTs

On drugs

Defining metabolic memory

JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

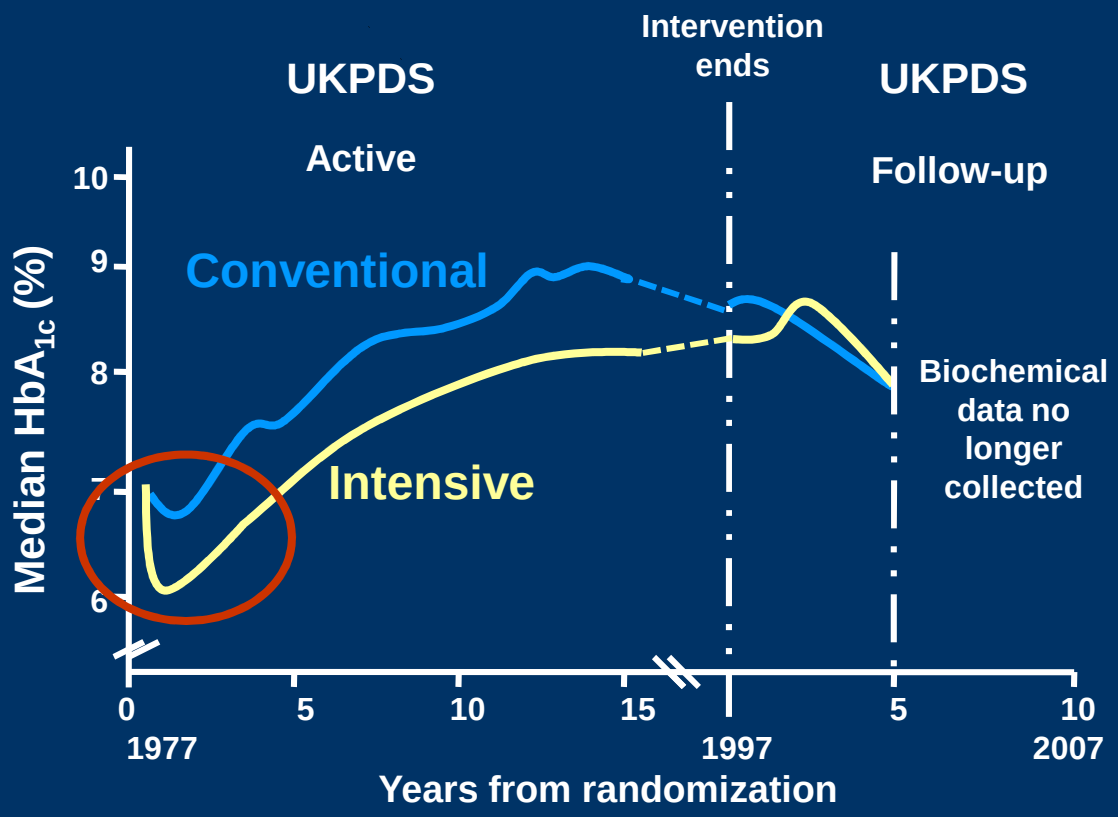
Antonio Ceriello, Michael A. Ihnat and Jessica E. Thorpe

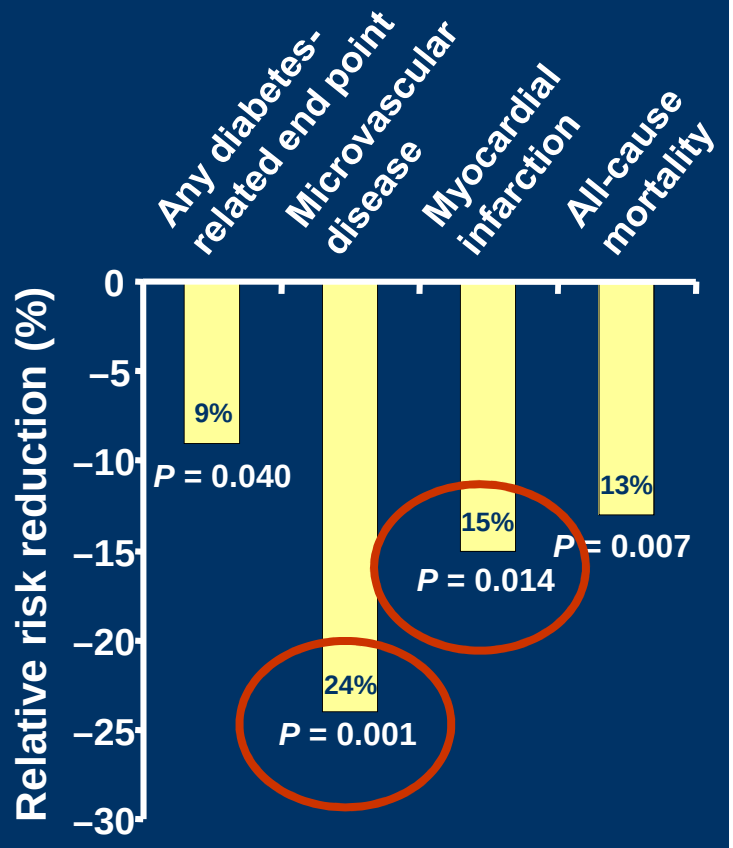
- *"Epidemiological and prospective data support a long-term influence of early metabolic control on clinical outcomes"*
- *"...early glycaemic environment is remembered in the target organs (i.e., eye, kidney, heart, extremities)"*

"The concept of a metabolic memory is of diabetic vascular stresses persisting after glucose normalization"

J Clin. Endocrinol. Metab. 2009 94:410-415

UKPDS: long-term follow-up and legacy effect





Bailey CJ & Day C. *Br J Diabetes Vasc Dis* 2008; **8:**242–247.
Holman RR, *et al*. *N Engl J Med* 2008; **359:**1577–1589.

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UKPDS: Legacy Effect of Earlier Glucose Control

After median 8.5 years post-trial follow-up

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

RRR = Relative Risk Reduction, P = Log Rank

Legacy Effect of Earlier Glucose Control

STANDARD ITALIANI PER LA CURA DEL DIABETE MELLITO

2009-2010

Follow-up a lungo termine degli studi DCCT e UKPDS suggeriscono che un trattamento volto a

o inferiore a 7% è generalmente consigliabile per i soggetti adulti con diabete per prevenire l'incidenza e la progressione delle complicanze macrovascolari.

ACCORD ADVANCE VADT
Research Question

Does Intensive Glucose Control Reduce Risk for Cardiovascular Disease in type 2 Diabetes?

ACCORD Study Group, NEJM 2008, 358:2545-2559
ADVANCE Collaborative Group, NEJM 2008, 258:2560-2572
VADT Study Results, Diabetes Obesity and Metabolism, 2008

ACCORD, ADVANCE and VADT Outcomes, intensive vs. standard

	ACCORD	ADVANCE	VADT
HbA1c %	6.4 vs. 7.5*	6.5 vs. 7.3*	6.9 vs. 8.4*
Death from any cause %	5.0 vs. 4.0*	8.9 vs. 9.6	NA
Death from cardiovascular event %	2.6 vs. 1.8*	4.5 vs. 5.2	2.1 vs. 1.7
Nonfatal MI %	3.6 vs. 4.6*	2.7 vs. 2.8	6.1 vs. 6.3
Nonfatal stroke %	1.3 vs. 1.2	3.8 vs. 3.8	2.0 vs. 3.1
New or worsening nephropathy %	NA	4.1 vs. 5.2*	NA
Major/severe hypoglycemia %	10.5 vs. 3.5*	2.7 vs. 1.5*	21.1 vs. 9.7*
Weight gain kg	3.5 vs. 0.4*	0.0 vs. -1.0*	NA

*$p \leq 0.05$

ACCORD ADVANCE VADT
Lesson Learned

- Intensive glucose control does not reduce CVD mortality in T2DM, and **may** increase risk, especially in patients with pre-existing CHD
- Aggressive HbA_1c target (< 6.5%) were associated with important increase of hypoglycemia
- Aggressive HbA_1c target (< 6.5%) are probably reasonable for **healthy patients** to reduce risk micro and macro vascular complications

ACCORD Study Group, NEJM 2008, 358:2545-2559
ADVANCE Collaborative Group, NEJM 2008, 258:2560-2572
VADT Study Results, Diabetes Obesity and Metabolism, 2008

Can long-term glycemic control reduce the risk of cardiovascular disease?

Yes	No
DCCT/EDIC	ACCORD
UKPDS Post-Trial Monitoring	ADVANCE
	VADT

E’ tempo per una terapia personalizzata

Reviews/Commentaries/ADA Statements
CONSENSUS STATEMENT

Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy

A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes

Nathan and Associates DIABETES CARE, VOLUME 29, NUMBER 8, AUGUST 2006

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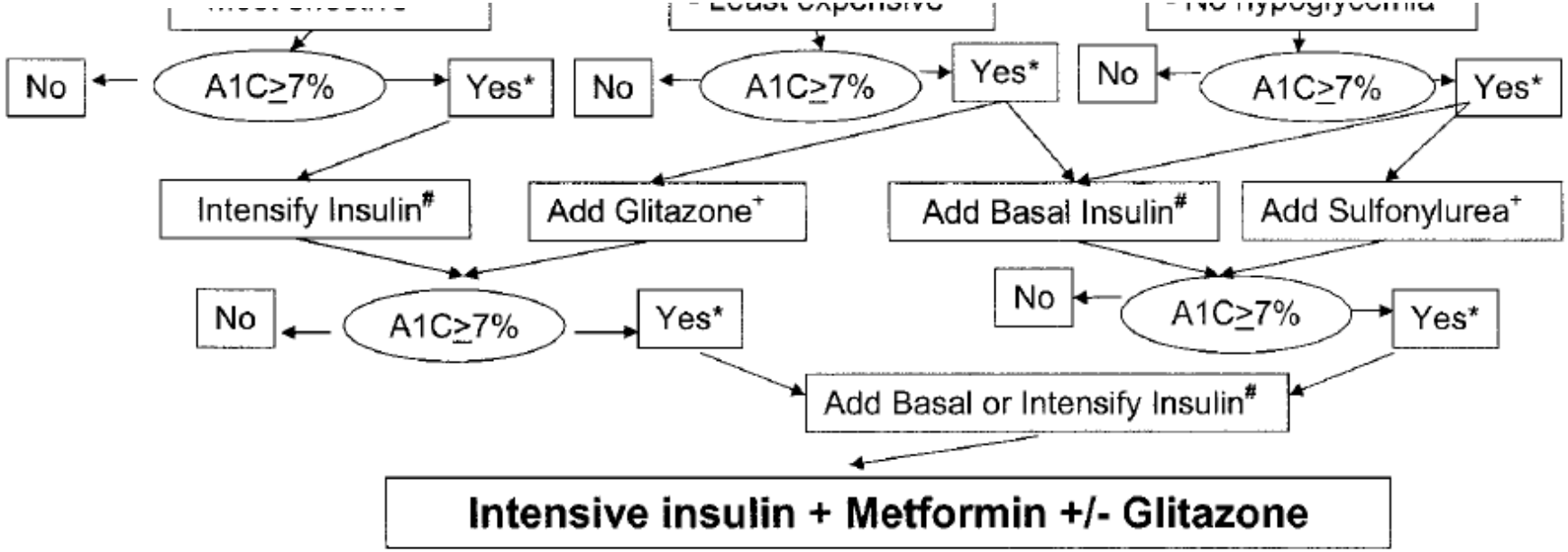
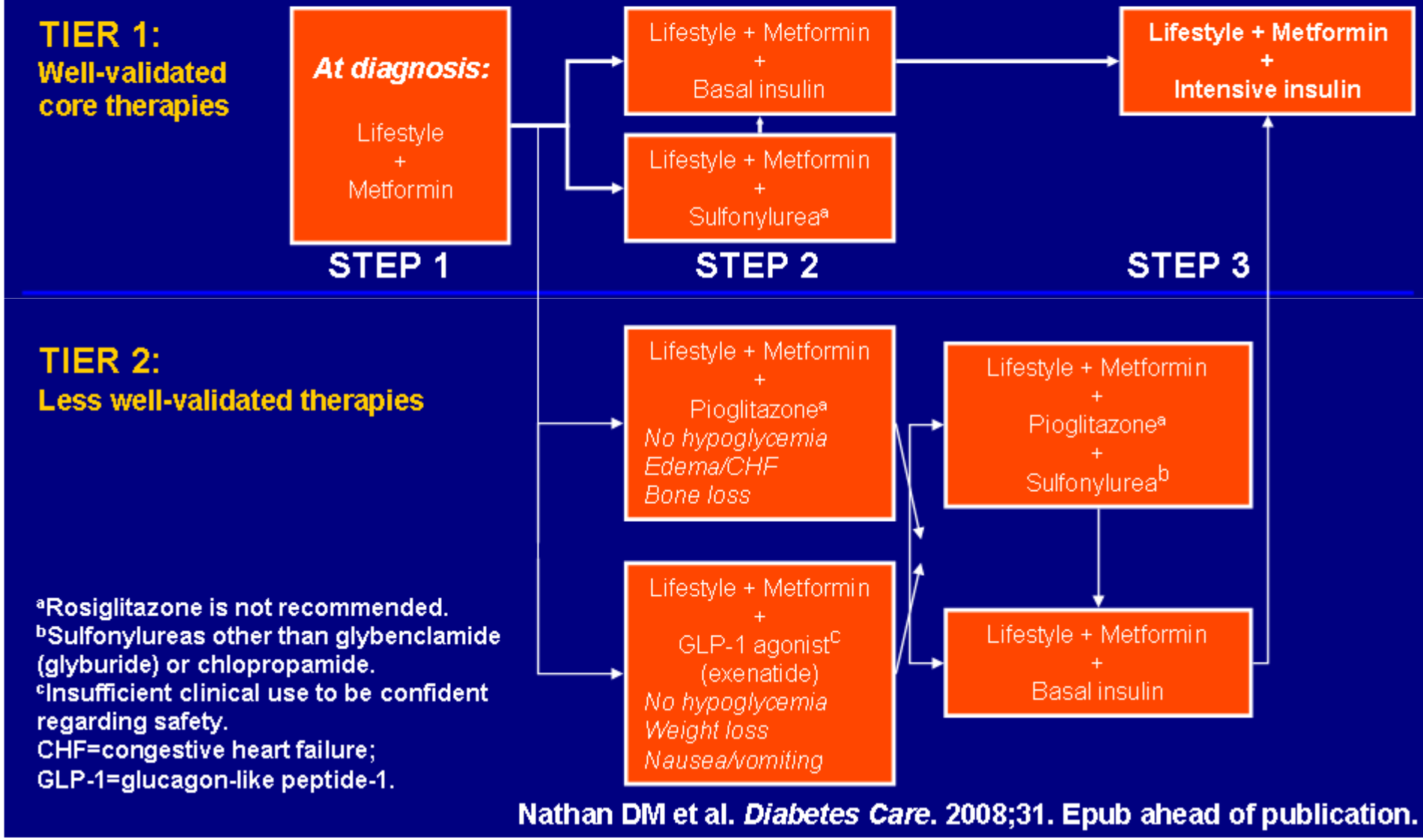


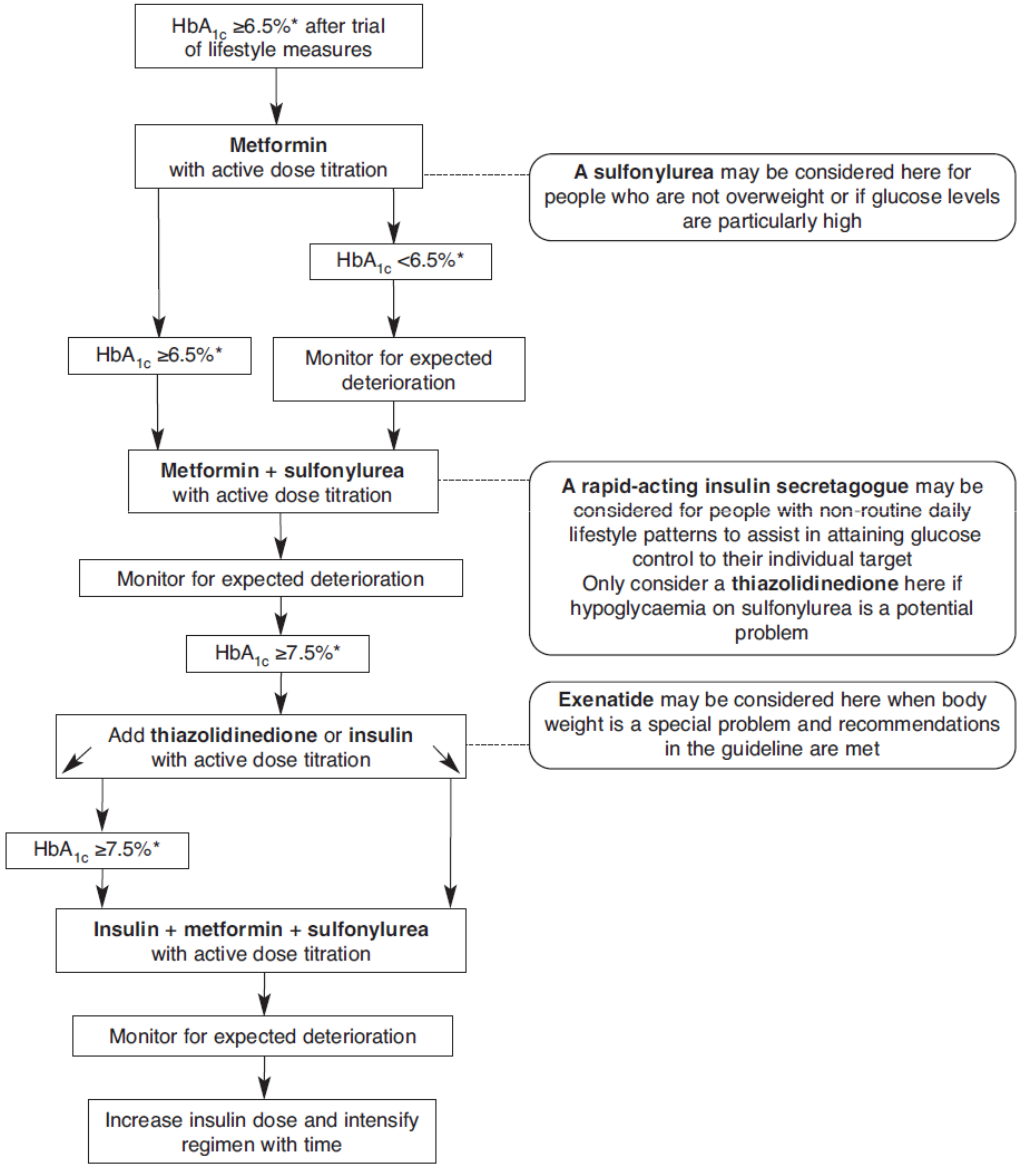
ADA/EASD: Metabolic Management of Type 2 Diabetes



[a]Rosiglitazone is not recommended.
[b]Sulfonylureas other than glybenclamide (glyburide) or chlopropamide.
[c]Insufficient clinical use to be confident regarding safety.
CHF=congestive heart failure;
GLP-1=glucagon-like peptide-1.

Nathan DM et al. *Diabetes Care*. 2008;31. Epub ahead of publication.

3.2 Algorithms



The National Collaborating Centre for Chronic Conditions

Funded to produce guidelines for the NHS by NICE

TYPE 2 DIABETES

National clinical guideline for management in primary and secondary care (update)

NHS National Institute for Health and Clinical Excellence

STANDARD ITALIANI PER LA CURA DEL DIABETE MELLITO

2009-2010

- Il trattamento del diabete deve essere tempestivamente adattato in ogni paziente fino a ottenere valori di HbA_{1c} stabilmente inferiori a 7% (Tabella 9), valori che consentono di prevenire l'incidenza e la progressione delle complicanze microvascolari. (**Livello della prova I, Forza della raccomandazione A**)

- Obiettivi glicemici più stringenti ($HbA_{1c} \leq 6,5\%$) dovrebbero essere perseguiti in pazienti di nuova diagnosi o con diabete di durata < 10 anni, senza precedenti di CVD abitualmente in discreto compenso glicemico e senza comorbilità che li rendano particolarmente fragili. (**Livello della prova III, Forza della raccomandazione A**)

STANDARD ITALIANI PER LA CURA DEL DIABETE MELLITO

2009-2010

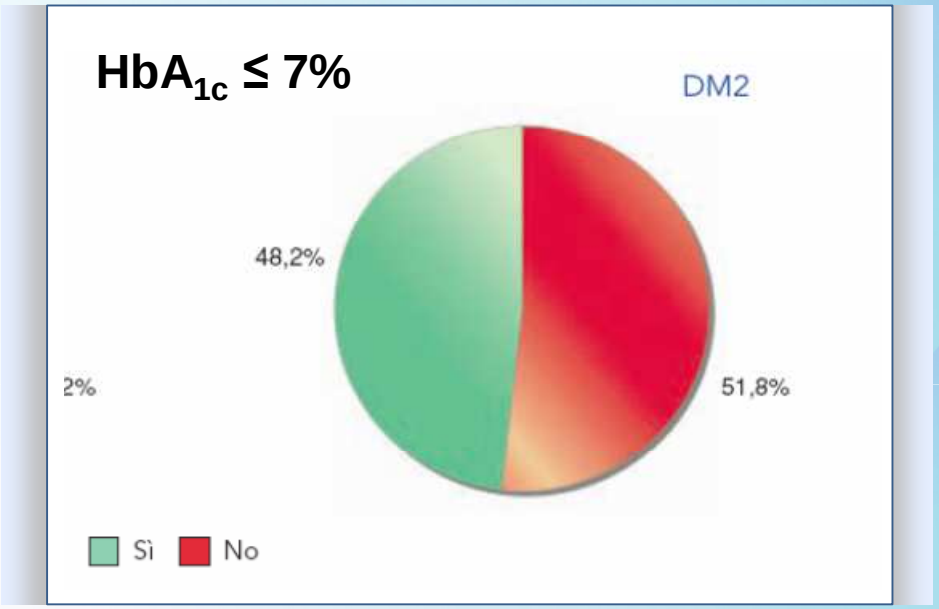
Obiettivi di compenso glicemico meno stringenti (HbA_{1c} 7-8%) dovrebbero essere perseguiti in pazienti con diabete di lunga durata > 10 anni soprattutto con precedenti di CVD o una lunga storia di inadeguato compenso glicemico o fragili per età e/o comorbilità. L'approccio terapeutico deve essere tale da prevenire le ipoglicemie. (**Livello della prova VI, Forza della raccomandazione B**)

STANDARD ITALIANI PER LA CURA DEL DIABETE MELLITO 2009-2010

RACCOMANDAZIONI

- Perseguire lo stretto controllo della glicemia al fine di ridurre il rischio di insorgenza o peggioramento delle complicanze microvascolari. (**Livello della prova I, Forza della raccomandazione A**)
- Perseguire lo stretto controllo della glicemia sin dalla diagnosi al fine di ridurre le complicanze cardiovascolari a lungo termine. (**Livello della prova II, Forza della raccomandazione A**)
- In presenza di valori di HbA_{1c} superiori all'obiettivo glicemico è necessario mettere tempestivamente in atto le opportune variazioni della terapia finalizzate a raggiungere e mantenere nel tempo il buon controllo glicemico. (**Livello della prova II, Forza della raccomandazione B**)
- Il farmaco di prima scelta per il trattamento dei diabetici tipo 2 è la metformina: in presenza di sovrappeso (**Livello della prova II, Forza della raccomandazione A**) e di normopeso (**Livello della prova VI, Forza della raccomandazione B**)
- Metformina, glitazoni, sulfoniluree, repaglinide, inibitori DPP-4 e analoghi del GLP-1 sono parimenti efficaci nel ridurre l'emoglobina glicosilata, ma meno efficaci rispetto all'insulina. (**Livello della prova I, Forza della raccomandazione A**)
- In molti pazienti, non in buon controllo in monoterapia, è necessario associare due o più farmaci. (**Livello della prova I, Forza della raccomandazione A**)
- Quando il controllo della glicemia non è soddisfacente, anche in politerapia, è necessario iniziare la terapia insulinica mono- o multiniettiva. (**Livello della prova I, Forza della raccomandazione A**)
- Tenere in considerazione la possibile scarsa adesione alla terapia prescritta. (**Livello della prova I, Forza della raccomandazione A**)

Annali AMD: ancora inerzia terapeutica e mancato raggiungimento obiettivi terapeutici



HbA_{1c}:

- Valore medio 7,3%
- 17% valori sotto 6%
- 25% valori sopra 8%
- 60% ha valori tra 6 e 8%

La metà dei pazienti ha la HbA_{1c} >7,0%!
difficoltà di un controllo adeguato

Il paziente in ipo orali ha in media 7,3% di HbA_{1c}
Il valore aumenta in pazienti politrattati

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per la cura del diabete mellito
2014

DMT2 e terapia insulinica

- Il DMT2 è caratterizzato da un progressivo declino della massa della funzione betacellulare
- Già al momento della diagnosi circa il 50% della funzione betacellulare è perduto con una ulteriore perdita di funzione del 4-6% per anno
- La terapia insulinica inoltre nel DMT2 corregge la glucotossicità e la lipotossicità e migliora l'azione periferica dell'insulina

Pertanto in una fase più o meno precoce della storia naturale del DMT2 la terapia insulinica è necessaria

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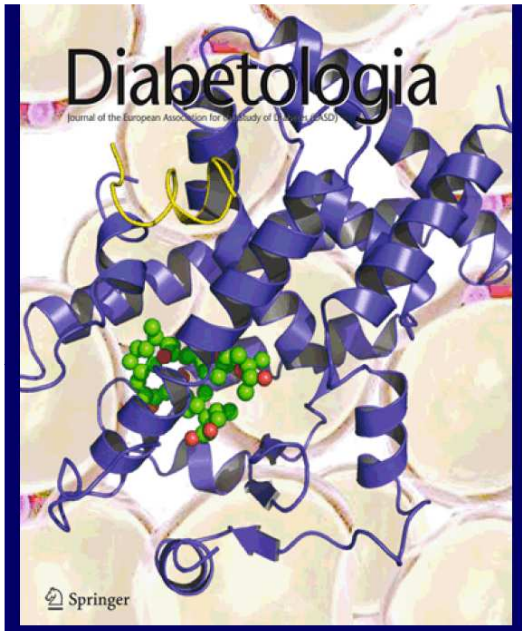
2014

DMT2 e terapia insulinica

Poichè la maggior parte dei soggetti con DMT2 mantiene una residua capacità di secernere insulina anche in stadi avanzati della malattia, il trattamento insulinico del DMT2 non richiede all'inizio i complessi e intensivi schemi di trattamento tipici del DMT1

Idealmente il trattamento insulinico dovrebbe essere in grado di ottenere un buon controllo metabolico con il minore rischio possibile di ipoglicemia e d'incremento ponderale e con un semplice regime di titolazione



Diabetologia
DOI 10.1007/s00125-012-2534-0

POSITION STATEMENT

Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

S. E. Inzucchi · R. M. Bergenstal · J. B. Buse · M. Diamant · E. Ferrannini · M. Nauck · A. L. Peters · A. Tsapas · R. Wender · D. R. Matthews

Insulin Due to the progressive beta cell dysfunction that characterises type 2 diabetes, insulin replacement therapy is frequently required [71]. Importantly, most patients maintain some endogenous insulin secretion even in late stages of disease. Accordingly, the more complex and intensive strategies of type 1 diabetes are not typically necessary [72].

Ideally, the principle of insulin use is the creation of as normal a glycaemic profile as possible without unacceptable weight gain or hypoglycaemia [73]. As initial therapy, unless the patient is markedly hyperglycaemic and/or symptomatic, a 'basal' insulin alone is typically added [74].

Gli standard italiani

Standard italiani
per la cura del diabete mellito
2014

Terapia con insulina del diabete di tipo 2

1. Iniziare la terapia con insulina quando la terapia ipoglicemizzante non insulinica e l'intervento sullo stile di vita non sono in grado di ottenere il controllo della glicemia. Mantenere tuttavia sempre il supporto per il mantenimento dello stile di vita. Considerare l'inizio o l'aumento dell'insulina ogni 2-6 mesi, con l'obiettivo di raggiungere e mantenere nel tempo valori di HbA_{1c} prestabiliti, in genere <53 mmol/mol o 7%.

2. Spiegare al paziente affetto da diabete sin dal momento della diagnosi che l'insulina è comunque una delle possibili terapie e che può rivelarsi la migliore, oppure l'unica, per raggiungere o mantenere il controllo della glicemia.

3. Iniziare un percorso di educazione terapeutica e prescrivere l'uso di presìdi per l'automonitoraggio. Spiegare che all'inizio le dosi prescritte possono essere basse ma che in alcuni casi si può giungere a 50-100 Unità/die.

4. Iniziare la terapia insulinica prima della comparsa dello scompenso metabolico, in particolare iniziare quando, nonostante una terapia massimale, l'HbA_{1c} (dosaggio standardizzato con lo studio DCCT) supera di >0,5% gli obiettivi glicemici. Continuare comunque la metformina. L'uso dei secretagoghi può essere continuato, almeno temporaneamente, durante la terapia insulinica. Anche l'acarbosio può essere continuato. Prestare attenzione all'associazione con pioglitazone per l'aumentata ritenzione di liquidi.

Gli standard italiani

Standard italiani
per la cura del diabete mellito
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5. Quando si avvia la terapia insulinica:

5.1. Iniziare preferibilmente con un'insulina basale come glargine, detemir, ILPS o umana NPH (con umana NPH il rischio di ipoglicemia è tuttavia maggiore), tenendo comunque in considerazione le diverse farmacocinetiche

oppure, in seconda analisi

5.2. Utilizzare direttamente uno schema basal-bolus

oppure, in terza analisi

5.3. Utilizzare un analogo rapido ai pasti

oppure, in casi particolari,

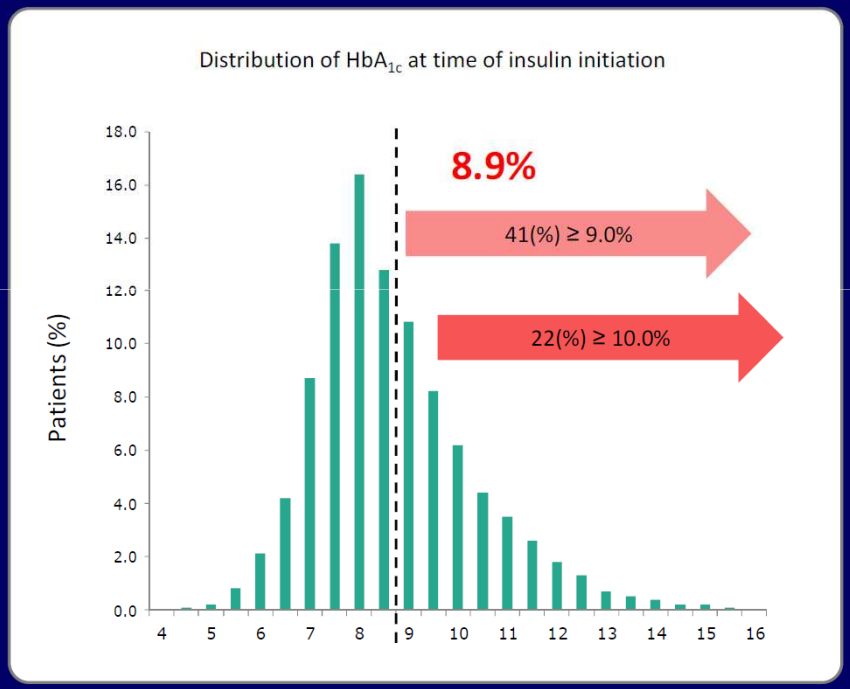
5.4. In presenza di gravi ed evidenti problemi di compliance, utilizzare una doppia somministrazione di insulina premiscelata (bifasica), tentando comunque di educare il paziente verso uno schema basal-bolus.

6. Iniziare l'insulina prescrivendo un regime di autotitolazione (aumento di 2 unità ogni 3 giorni fino all'obiettivo) oppure attraverso contatti settimanali (usando comunque uno schema simile). Controllare la glicemia anche negli altri momenti per identificare possibili altre cause di cattivo controllo.

7. Continuare il supporto al paziente, anche attraverso contatti telefonici, fino al raggiungimento dell'obiettivo glicemico.

8. Incoraggiare la somministrazione dell'insulina nel tessuto sottocutaneo della regione addominale (assorbimento veloce) e coscia (lento), considerando comunque braccio e glutei come valide alternative. Ricordarsi sempre che alcuni pazienti potrebbero non prediligere la somministrazione dell'insulina nella regione addominale per motivi culturali.

C’è una necessità di iniziare la terapia insulinica più precocemente



Khunti et al Diabetologia 2011; 54 (Suppl.1): S160 and Poster 377-P. 13 September 12:30-13:30, PS 013

L’inerzia clinica esiste nonostante:

Siano noti i benefici di un controllo controllo glicemico tempestivo

Le linee guida incoraggino un uso precoce dell’insulina

All’avvio della terapia insulinica nello studio SOLVE™:

L’ HbA1c media era 8,9%

41% had HbA1c ≥ 9,0%

22% had HbA1c ≥ 10,0%

Utilizzo precoce di terapia insulinica nel DMT2 e prevenzione CV

Standard italiani
per la cura del diabete mellito
2014

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Basal Insulin and Cardiovascular and Other Outcomes in Dysglycemia

The ORIGIN Trial Investigators*

ABSTRACT

N ENGL J MED 367;4 NEJM.ORG JULY 26, 2012

ORIGIN Outcome Reduction with Initial Glargine Intervention

BACKGROUND

The provision of sufficient basal insulin to normalize fasting plasma glucose levels may reduce cardiovascular events, but such a possibility has not been formally tested.

METHODS

We randomly assigned 12,537 people (mean age, 63.5 years) with cardiovascular risk factors plus impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes to receive insulin glargine (with a target fasting blood glucose level of ≤95 mg per deciliter [5.3 mmol per liter]) or standard care and to receive n–3 fatty acids or placebo with the use of a 2-by-2 factorial design. The results of the comparison between insulin glargine and standard care are reported here. The coprimary outcomes were nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes and these events plus revascularization or hospitalization for heart failure. Microvascular outcomes, incident diabetes, hypoglycemia, weight, and cancers were also compared between groups.

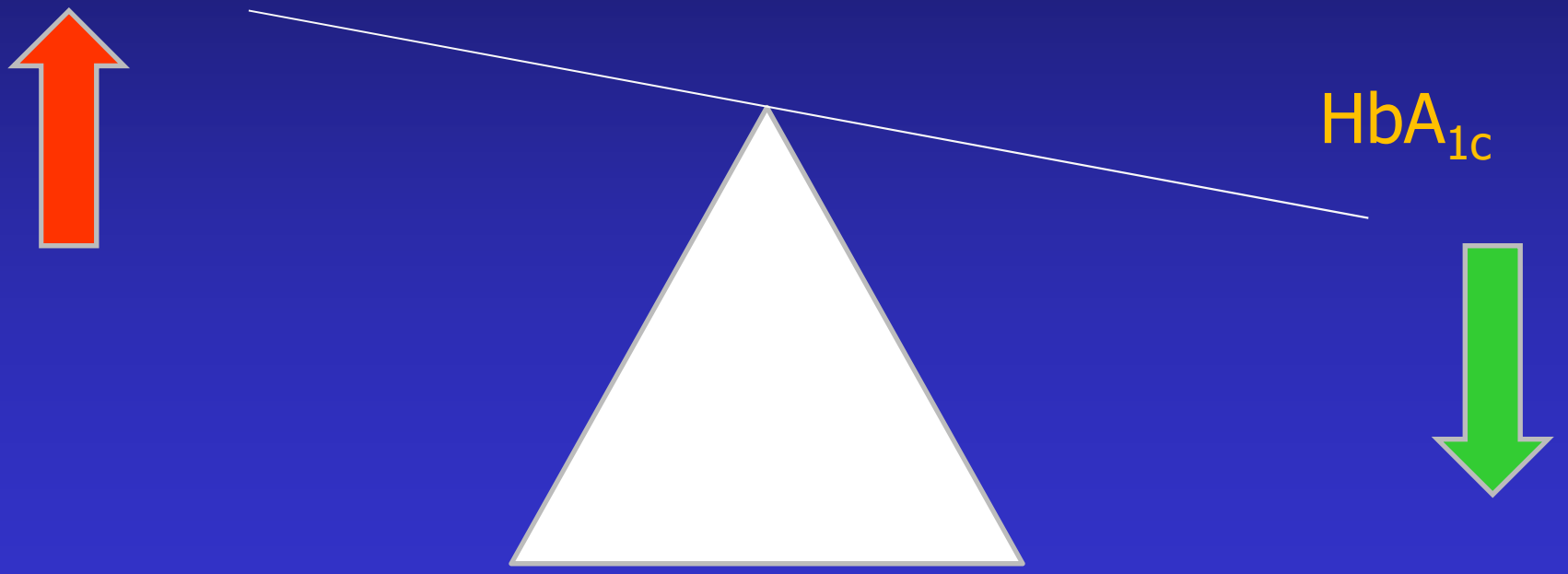
CONCLUSIONS

When used to target normal fasting plasma glucose levels for more than 6 years, insulin glargine had a neutral effect on cardiovascular outcomes and cancers. Although it reduced new-onset diabetes, insulin glargine also increased hypoglycemia and modestly increased weight. (Funded by Sanofi; ORIGIN ClinicalTrials.gov number, NCT00069784.)

ORIGIN Outcome Reduction with Initial Glargine Intervention

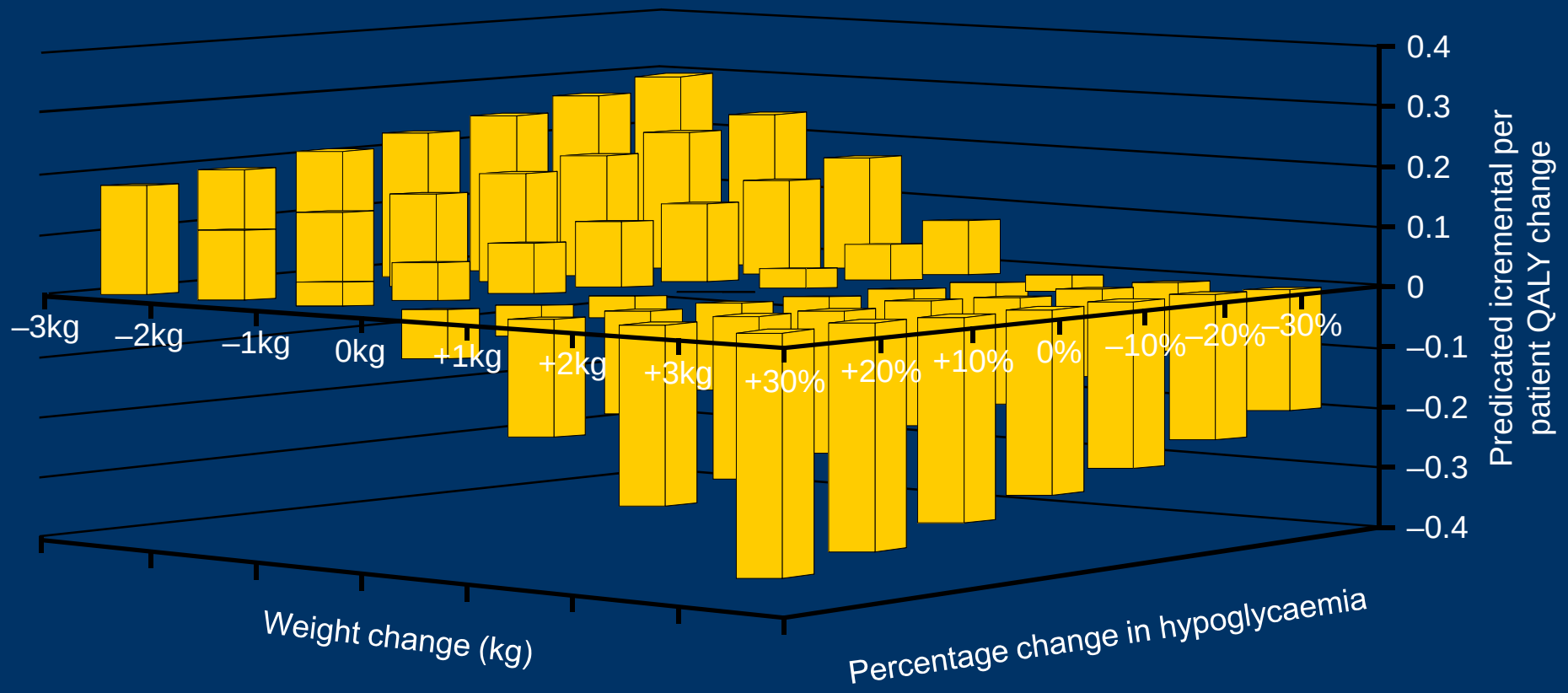
The challenge of blood glucose control

Hypoglycaemia/Weight gain/Quality of life



HbA_{1c}

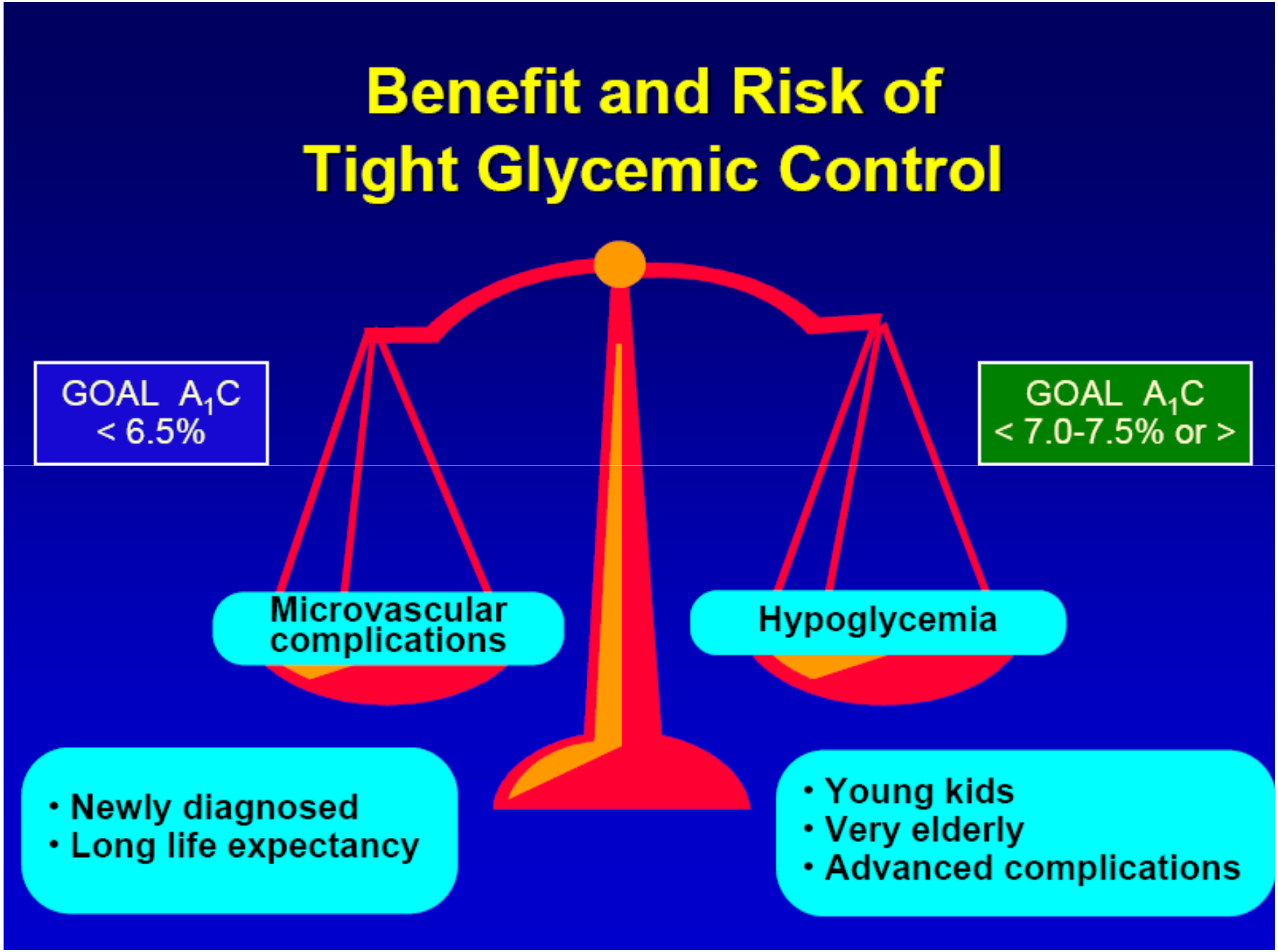
Relationship between weight gain, hypoglycaemia and quality of life



The graph illustrates that the QALY decrement associated with an increase in weight and hypoglycaemia by approximately 3 kg and 30%, respectively, will offset the QALY gain associated with a 1% reduction in HbA_{1c}

QALY: quality-adjusted life year

McEwan et al. Diabetes Obes Metab 2010;12:431–6


Benefit and Risk of
Tight Glycemic Control
GOAL A_1C
< 6.5%
GOAL A_1C
< 7.0-7.5% or >
Microvascular complications
Hypoglycemia
• Newly diagnosed
• Long life expectancy
• Young kids
• Very elderly
• Advanced complications

Efficacy in Type 2 Diabetes

Agent	HbA_{1c} Change
Insulin	1.5-3.5
Sulfonylureas	1.0-2.0
Metformin	1.0-2.0
Glinides	1.0-1.5
Thiazolidinediones	0.5-1.4
Exenatide	0.5-1.0
Acarbose	0.5-0.8
Vildagliptin	0.5-0.8

Nathan DM et al, *Diabetologia*, 2008

Criteri di selezione dei farmaci ipoglicemizzanti

Criteri Considerati nell'Algoritmo ADA/EASD

- Efficacia nel correggere iperglicemia *HbA_{1c}*
- Effetti extra-glicemici
  → *riduzione complicanze*
- Sicurezza
- Tollerabilità
- Costo

Altri Criteri Non Considerati

- Efficacia nel correggere iperglicemia
  FGP vs. PPG
- *"Durability"*
- Fenotipo del paziente
  clinico (BMI, waist, ±SM, ±CVD)
  glicemico
- Meccanismo patogenetico
  deficit secrezione vs. insulino-resistenza, autoimmunità

Therapeutic Goals in Type 2 Diabetes

- To lower HbA_1c levels
- To reduce fasting and post-prandial glucose levels
- To control traditional (BP, lipids, smoking) and non traditional (CRP, PAI-1, AER) CV risk factors
- To reduce CV events and mortality
- To lower the incidence of microvascular disease
- To improve the quality of life
- To preserve β-cell mass
- To delay progression of disease
- To avoid weight gain
- To meet patient's compliance (administration of drugs, hypoglycemia, etc.)

Therapeutic Goals in Type 2 Diabetes

- L'intervento terapeutico deve essere tempestivo e precoce (Early)
- È necessario impedire il deterioramento progressivo dell'HbA1c
- Modificare la terapia entro 2 mesi oltre i 3 mesi (no Inerzia Terapeutica)
- Prestare attenzione ad altri fattori di rischio (PA, fumo, lipidi) e agli effetti collaterali (ipoglicemie, aumento di peso)
- Favorire la compliance del paziente incontrando i bisogni individuali

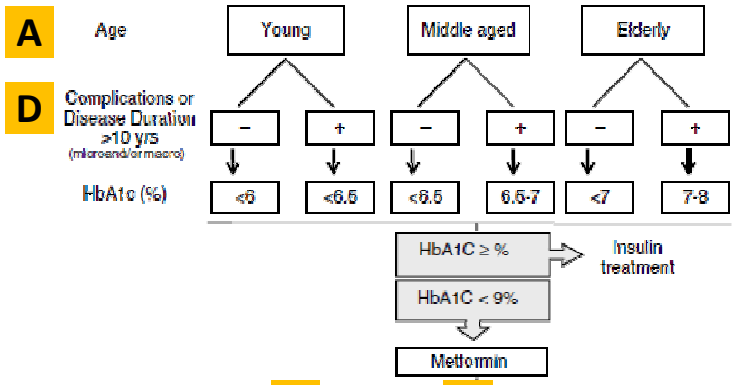
Personalizzazione della terapia

A1C and ABCD

The A1C and ABCD of glycaemia management in type 2 diabetes: a physician's personalized approach

Paolo Pozzilli[1,2†]
R. David Leslie[2,3*†]
Juliana Chan[4] Ralph De Fronzo[5]
Louis Monnier[6] Itamar Raz[7]
Stefano Del Prato[8]

Diabetes Metab Res Rev 2010



B C

Physician should choose drug according to patient's risk of weight gain, hypoglycaemia, cardio-renal complications

Class	Effect on Body Weight	Risk of Hypoglycaemia	Cardio-renal Complications: Contraindications
Metformin	Weight loss	Negligible as monotherapy	Moderate renal failure; Heart failure
GLP1 analogues	Weight loss	Negligible as monotherapy	Severe renal failure
DPPIV inhibitors	Neutral	Negligible as monotherapy	Severe renal failure
Glucosidase inhibitors	Neutral	Negligible as monotherapy	Severe renal failure
Thiazolidinediones	Weight gain	Negligible as Monotherapy	Renal Failure; Heart failure (class III or IV)
Insulin analogues: Rapid-acting analogues Long-acting analogues	Weight gain (rapid-acting > long-acting)	High risk Minimal risk	
Sulphonylureas	Weight gain	Minimal to significant (depending on agent)	Moderate renal failure
Glinides	Weight gain	Minimal/moderate	

Strategy	Glycaemic goal	Time frame to reach glycaemic goal	At presentation: Mild hyperglycaemia Definition	At presentation: Mild hyperglycaemia Type of intervention	At presentation: Severe hyperglycaemia Definition	At presentation: Severe hyperglycaemia Type of intervention	Add-on therapy to metformin: Principles in selecting interventions	Add-on therapy to metformin: Drugs excluded
ABCD	Individualized <6–8%[a]	Individualized 3–12 months[a]	A1C <9%	Lifestyle + metformin	A1C ≥9%	Insulin	Age body weight; complications; diabetes duration	–

ABCD, age, body weight, complications and duration of disease.

AACE/ACE Diabetes Algorithm *For Glycemic Control*

A1C Goal ≤ 6.5%*

LIFESTYLE MODIFICATION

A1C 6.5 – 7.5%**

Monotherapy

MET †	DPP4 [1]	GLP-1	TZD [2]	AGI [3]

2 - 3 Mos.***

Dual Therapy

MET	+	GLP-1 or DPP4 [1]
		TZD [2]
		Glinide or SU [5]
TZD	+	GLP-1 or DPP4 [1]
MET	+	Colesevelam
		AGI [3]

2 - 3 Mos.***

Triple Therapy

MET + GLP-1 or DPP4 [1]	+	TZD [2]
		Glinide or SU [4,7]

2 - 3 Mos.***

INSULIN ± Other Agent(s) [6]

A1C 7.6 – 9.0%

Dual Therapy [8]

MET	+	GLP-1 or DPP4 [1] or TZD [2]
		SU or Glinide [4,5]

2 - 3 Mos.***

Triple Therapy [9]

MET	+	GLP-1 or DPP4 [1]	+ TZD [2]
		GLP-1 or DPP4 [1]	+ SU [7]
		TZD [2]	

2 - 3 Mos.***

INSULIN ± Other Agent(s) [6]

A1C > 9.0%

Drug Naive | *Under Treatment*

Symptoms | *No Symptoms*

INSULIN ± Other Agent(s) [6]

MET	+	GLP-1 or DPP4 [1]	± SU [7]
		TZD [2]	
		GLP-1 or DPP4 [1]	± TZD [2]

INSULIN ± Other Agent(s) [6]

AACE/ACE Algorithm for Glycemic Control Committee

Cochairpersons:
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* May not be appropriate for all patients

** For patients with diabetes and A1C < 6.5%, pharmacologic Rx may be considered

*** If A1C goal not achieved safely

† Preferred initial agent

1 DPP4 if ↑ PPG and ↑ FPG or GLP-1 if ↑↑ PPG

2 TZD if metabolic syndrome and/or nonalcoholic fatty liver disease (NAFLD)

3 AGI if ↑ PPG

4 Glinide if ↑ PPG or SU if ↑ FPG

5 Low-dose secretagogue recommended

6 a) Discontinue insulin secretagogue with multidose insulin
b) Can use pramlintide with prandial insulin

7 Decrease secretagogue by 50% when added to GLP-1 or DPP-4

8 If A1C < 8.5%, combination Rx with agents that cause hypoglycemia should be used with caution

9 If A1C > 8.5%, in patients on Dual Therapy, insulin should be considered

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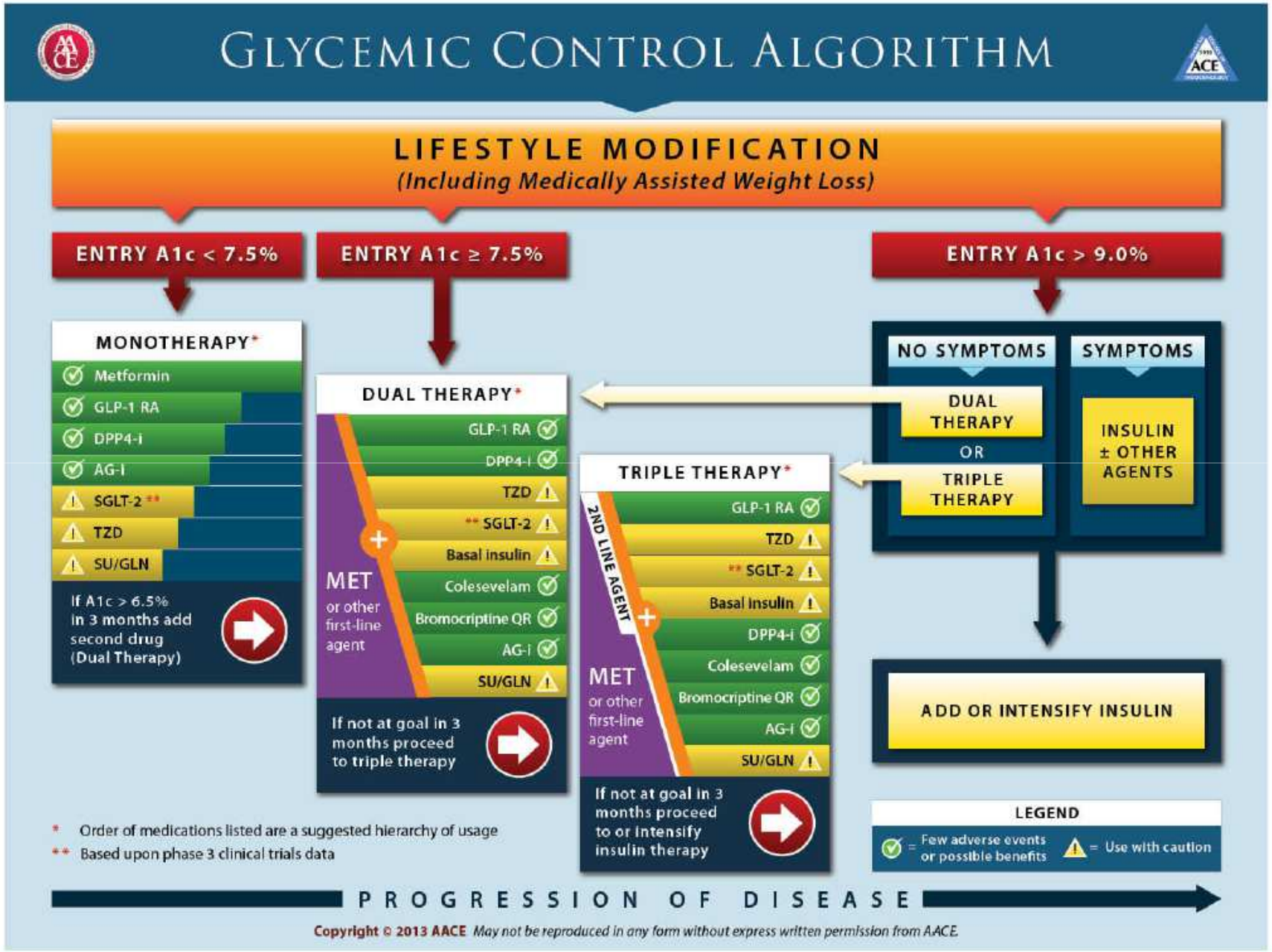
GLYCEMIC CONTROL ALGORITHM
LIFESTYLE MODIFICATION
(Including Medically Assisted Weight Loss)
ENTRY A1c < 7.5%
ENTRY A1c ≥ 7.5%
ENTRY A1c > 9.0%
MONOTHERAPY*
Metformin
GLP-1 RA
DPP4-i
AG-i
SGLT-2 **
TZD
SU/GLN
If A1c > 6.5% in 3 months add second drug (Dual Therapy)
DUAL THERAPY*
GLP-1 RA
DPP4-i
TZD
** SGLT-2
Basal insulin
Colesevelam
Bromocriptine QR
AG-i
SU/GLN
MET or other first-line agent
If not at goal in 3 months proceed to triple therapy
TRIPLE THERAPY*
2ND LINE AGENT
GLP-1 RA
TZD
** SGLT-2
Basal insulin
DPP4-i
Colesevelam
Bromocriptine QR
AG-i
SU/GLN
MET or other first-line agent
If not at goal in 3 months proceed to or intensify insulin therapy
NO SYMPTOMS
SYMPTOMS
DUAL THERAPY
OR
TRIPLE THERAPY
INSULIN ± OTHER AGENTS
ADD OR INTENSIFY INSULIN
LEGEND
= Few adverse events or possible benefits
= Use with caution
* Order of medications listed are a suggested hierarchy of usage
** Based upon phase 3 clinical trials data
PROGRESSION OF DISEASE
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TABLE 1

SUMMARY OF KEY BENEFITS AND RISKS OF MEDICATIONS

Benefits are classified according to major effects on fasting glucose, postprandial glucose, and nonalcoholic fatty liver disease (NAFLD). Eight broad categories of risks are summarized. The intensity of the background shading of the cells reflects relative importance of the benefit or risk.*

MEDICATIONS*	Metformin (MET)	DPP4 Inhibitor	GLP-1 Agonist (Incretin Mimetic)	Sulfonylurea (SU)	Glinide**	Thiazolidinedione (TZD)	Colesevelam	Alpha-glucosidase inhibitor (AGI)	Insulin	Pramlintide
BENEFITS										
Postprandial Glucose (PPG) - lowering	Mild	Moderate	Moderate to Marked	Moderate	Moderate	Mild	Mild	Moderate	Moderate to Marked	Moderate to Marked
Fasting glucose (FPG) - lowering	Moderate	Mild	Mild	Moderate	Mild	Moderate	Mild	Neutral	Moderate to Marked	Mild
Nonalcoholic fatty liver disease (NAFLD)	Mild	Neutral	Mild	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral
RISKS										
Hypoglycemia	Neutral	Neutral	Neutral	Moderate	Mild	Neutral	Neutral	Neutral	Moderate to Severe	Neutral
Gastrointestinal Symptoms	Moderate	Neutral	Moderate	Neutral	Neutral	Neutral	Moderate	Moderate	Neutral	Moderate
Risk of use with renal insufficiency	Severe	Reduce Dosage	Moderate	Moderate	Neutral	Mild	Neutral	Neutral	Moderate	Unknown
Contraindicated in Liver Failure or Predisposition to Lactic Acidosis	Severe	Neutral	Neutral	Moderate	Moderate	Moderate	Neutral	Neutral	Neutral	Neutral
Heart failure / Edema	Use with caution in CHF	Neutral	Neutral	Neutral	Neutral	Mild / Moderate Contraindicated in class 3,4 CHF	Neutral	Neutral	Neutral unless with TZD	Neutral
Weight Gain	Benefit	Neutral	Benefit	Mild	Mild	Moderate	Neutral	Neutral	Mild to Moderate	Benefit
Fractures	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral
Drug-Drug interactions	Neutral	Neutral	Neutral	Moderate	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral

* *The abbreviations used here correspond to those used on the algorithm (Fig. 1).*

** *The term 'glinide' includes both repaglinide and nateglinide.*

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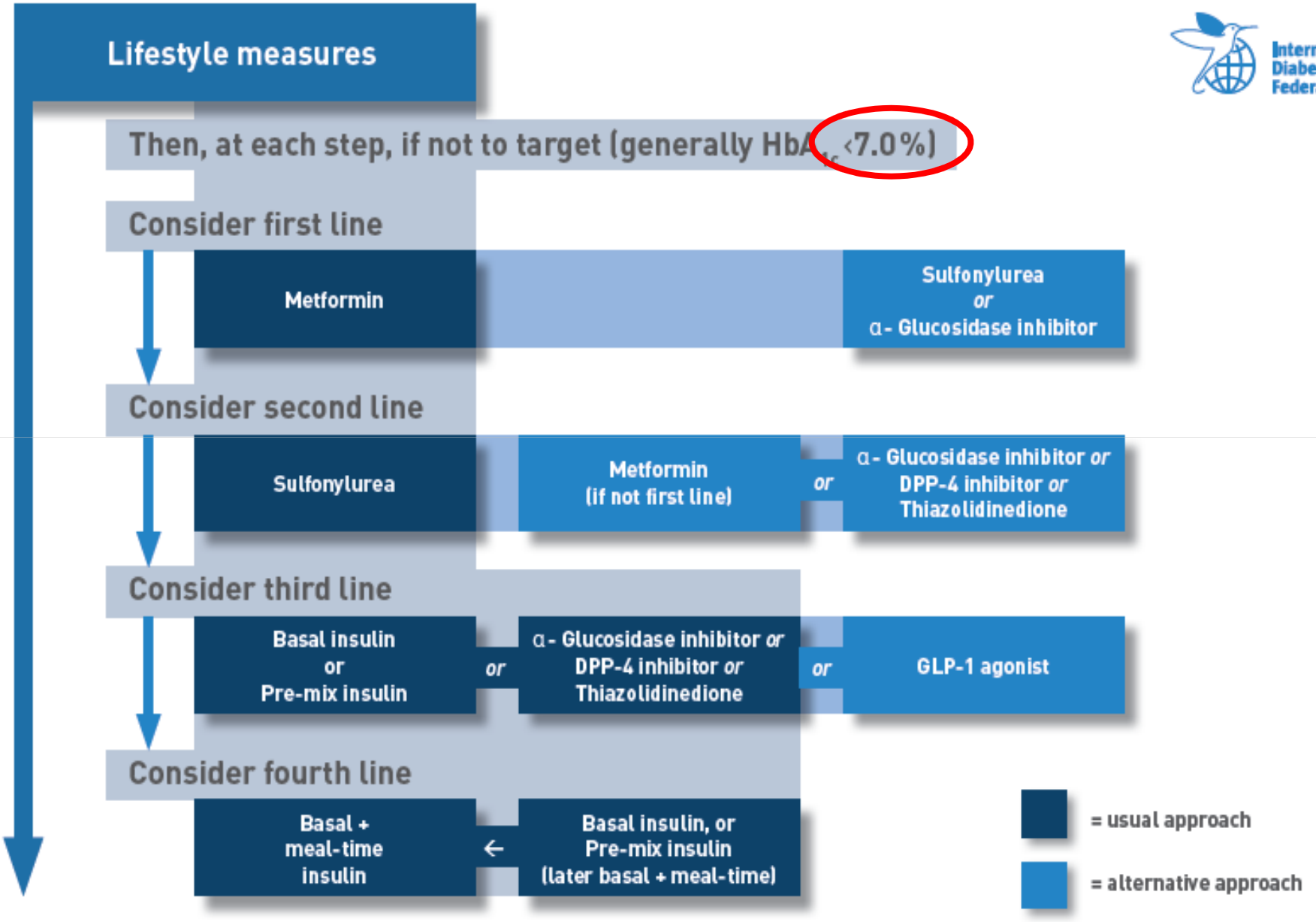
IDF Treatment Algorithm for People with Type 2 Diabetes



Personalizzazione della terapia nel Diabete Mellito tipo 2

Reviews/Consensus Reports/ADA Statements

POSITION STATEMENT

Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach

Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

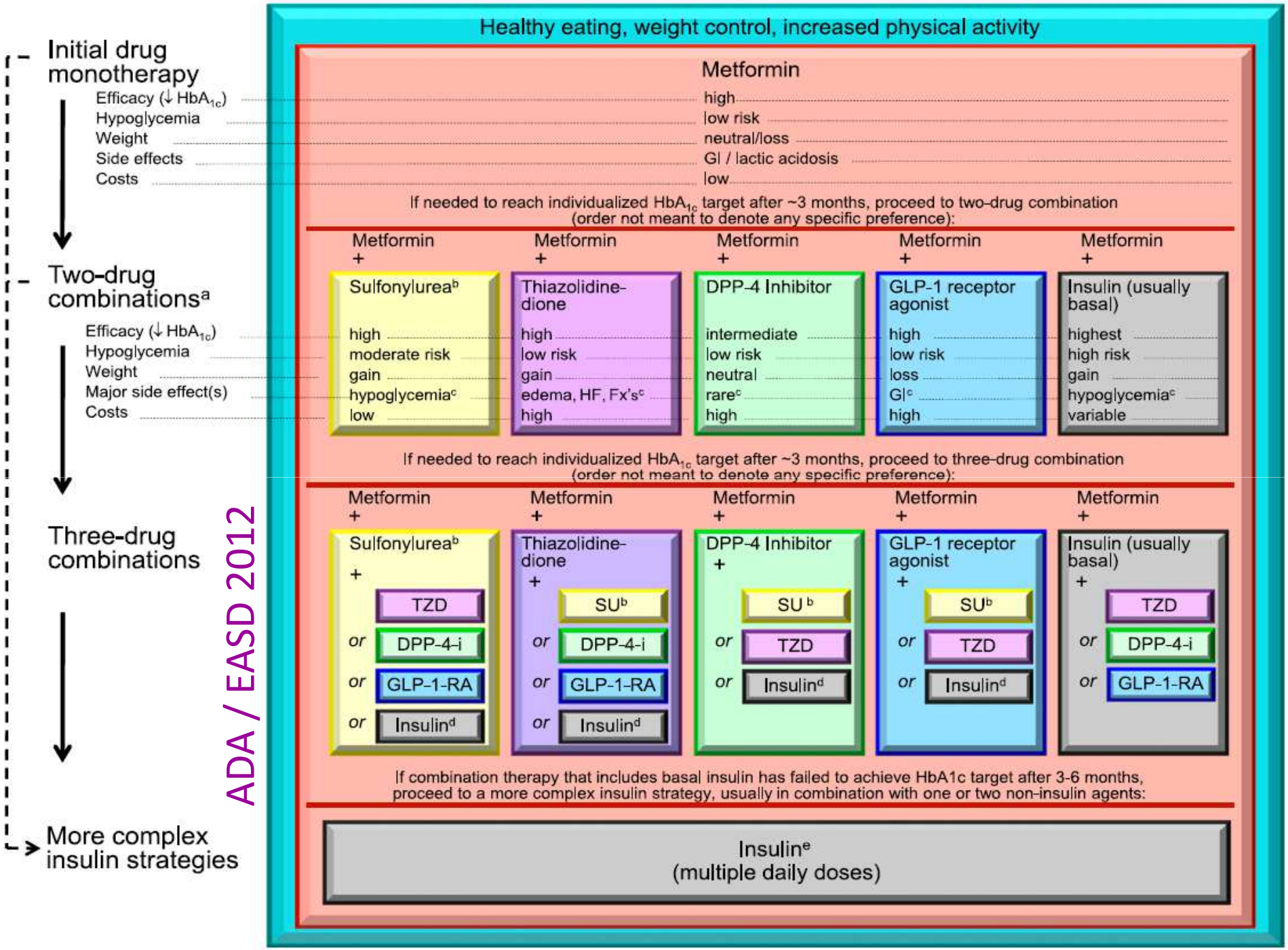
Silvio E. Inzucchi, MD[1]
Richard M. Bergenstal, MD[2]
John B. Buse, MD, PHD[3]
Michaela Diamant, MD, PHD[4]
Ele Ferrannini, MD[5]
Michael Nauck, MD[6]
Anne L. Peters, MD[7]
Apostolos Tsapas, MD, PHD[8]
Richard Wender, MD[9]
David R. Matthews, MD, DPHIL[10,11,12]

These recommendations should be considered within the context of the needs, preferences, and tolerances of each patient; individualization of treatment is the cornerstone of success. Our recommenda-

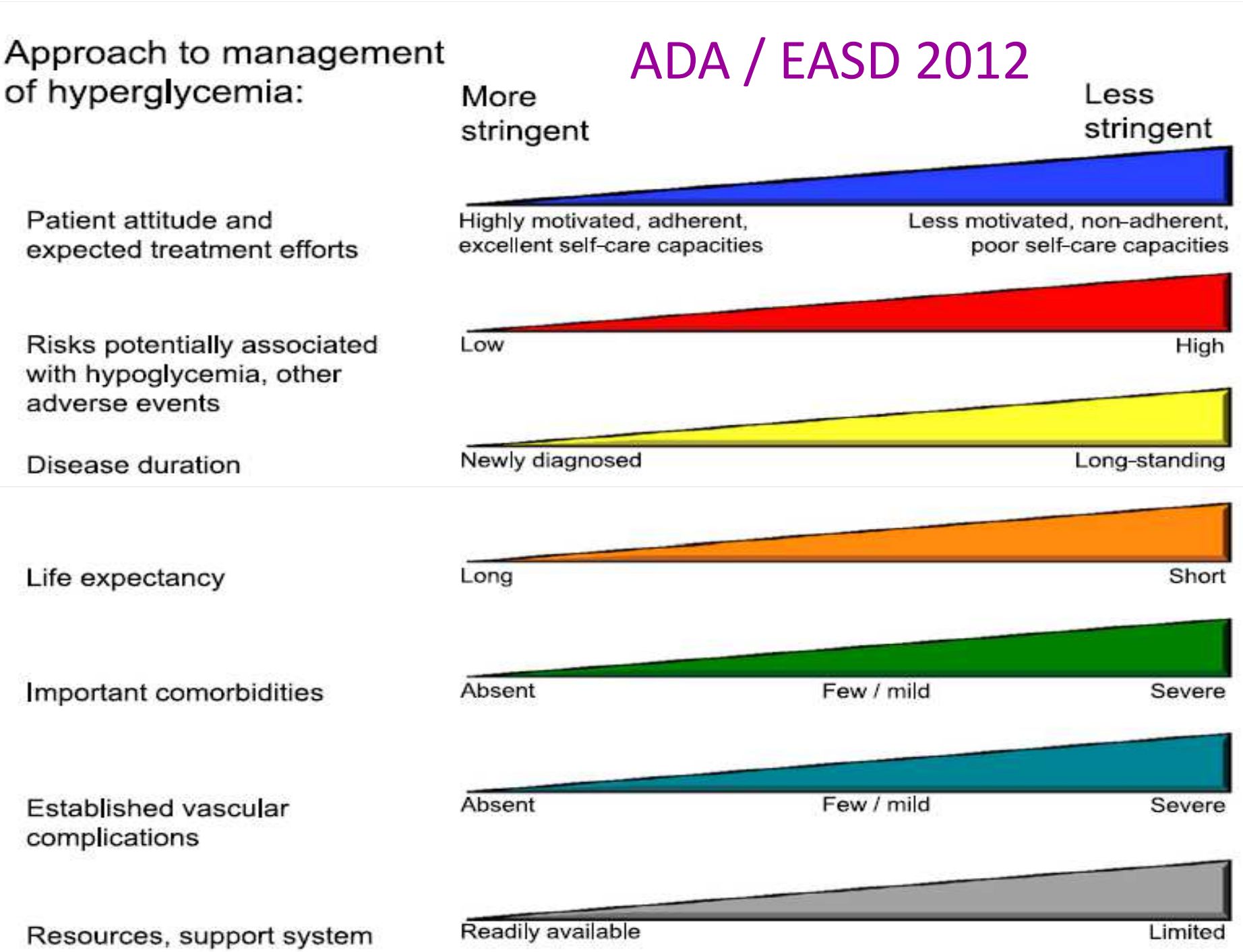
care.diabetesjournals.org

DIABETES CARE

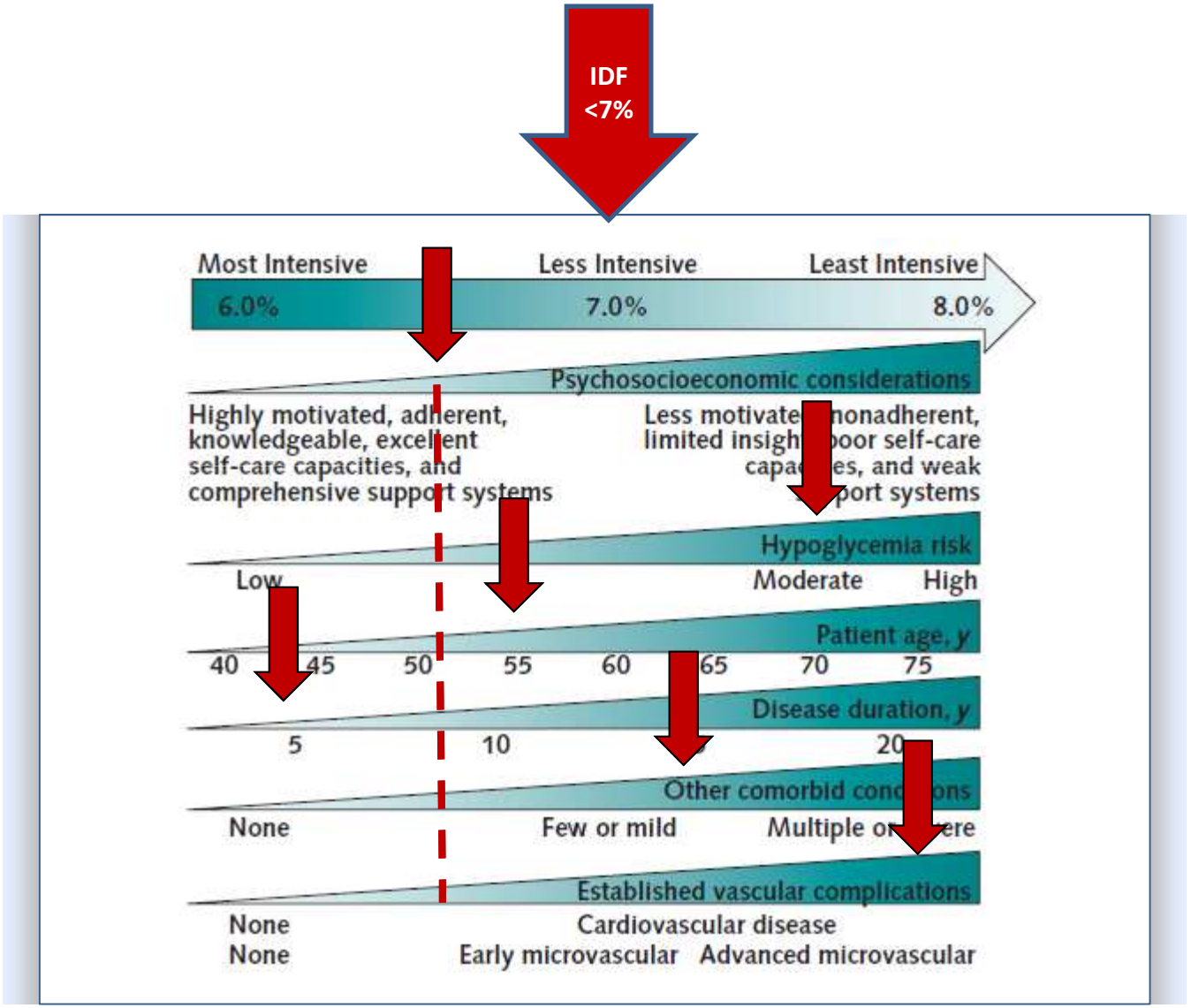
Diabetes Care Publish Ahead of Print, published online April 19, 2012


Healthy eating, weight control, increased physical activity
Initial drug monotherapy
Two-drug combinations[a]
Three-drug combinations
More complex insulin strategies
ADA / EASD 2012
Efficacy (↓ HbA1c)
Hypoglycemia
Weight
Side effects
Costs
Major side effect(s)
Metformin
high
low risk
neutral/loss
GI / lactic acidosis
low
If needed to reach individualized HbA1c target after ~3 months, proceed to two-drug combination
(order not meant to denote any specific preference):
Metformin +
Sulfonylurea[b]
high
moderate risk
gain
hypoglycemia[c]
low
Thiazolidine-dione
high
low risk
gain
edema, HF, Fx's[c]
high
DPP-4 Inhibitor
intermediate
low risk
neutral
rare[c]
high
GLP-1 receptor agonist
high
low risk
loss
GI[c]
high
Insulin (usually basal)
highest
high risk
gain
hypoglycemia[c]
variable
If needed to reach individualized HbA1c target after ~3 months, proceed to three-drug combination
(order not meant to denote any specific preference):
TZD
DPP-4-i
GLP-1-RA
Insulin[d]
SU[b]
or
If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3-6 months,
proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents:
Insulin[e]
(multiple daily doses)

ADA / EASD 2012

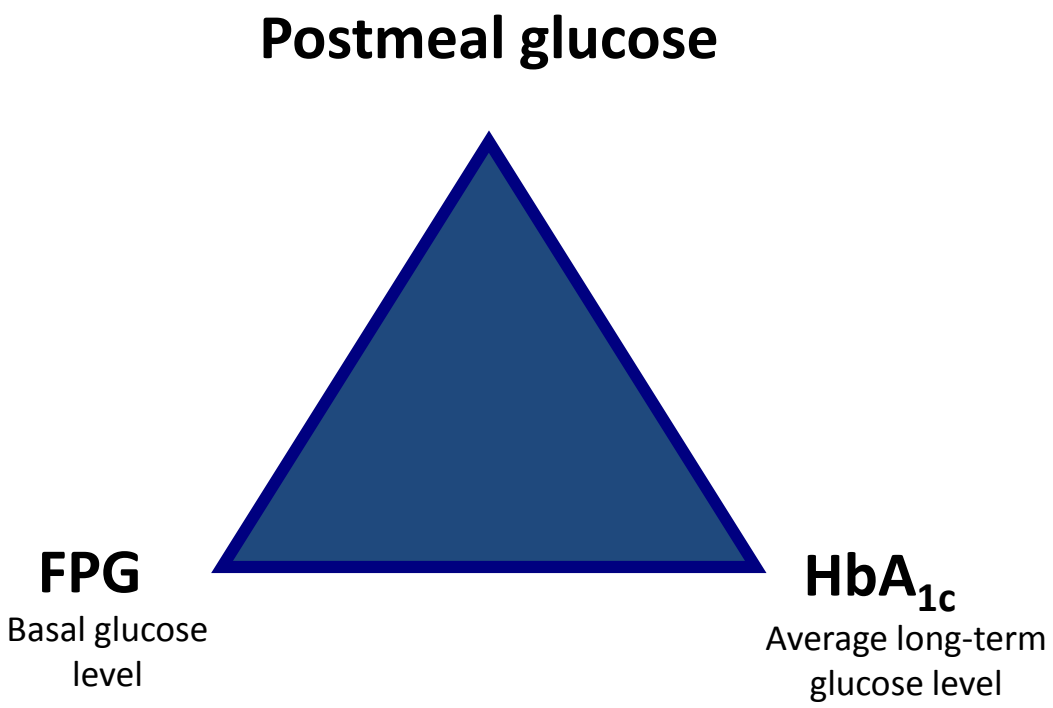


Come stabilire gli obiettivi di compenso glicemico nel paziente con diabete di tipo 2



Ismail-Beigi F. et al., Ann Int Med 2011

‘Glucose triad’ of diabetes management



Ceriello A. The glucose triad and its role in comprehensive glycaemic control: current status, future management Int J Clin Pract 2010;64(12):1705-1711

International Diabetes Federation

The Verona Study:
la prima segnalazione epidemiologica

Epidemiology/Health Services/Psychosocial Research
ORIGINAL ARTICLE

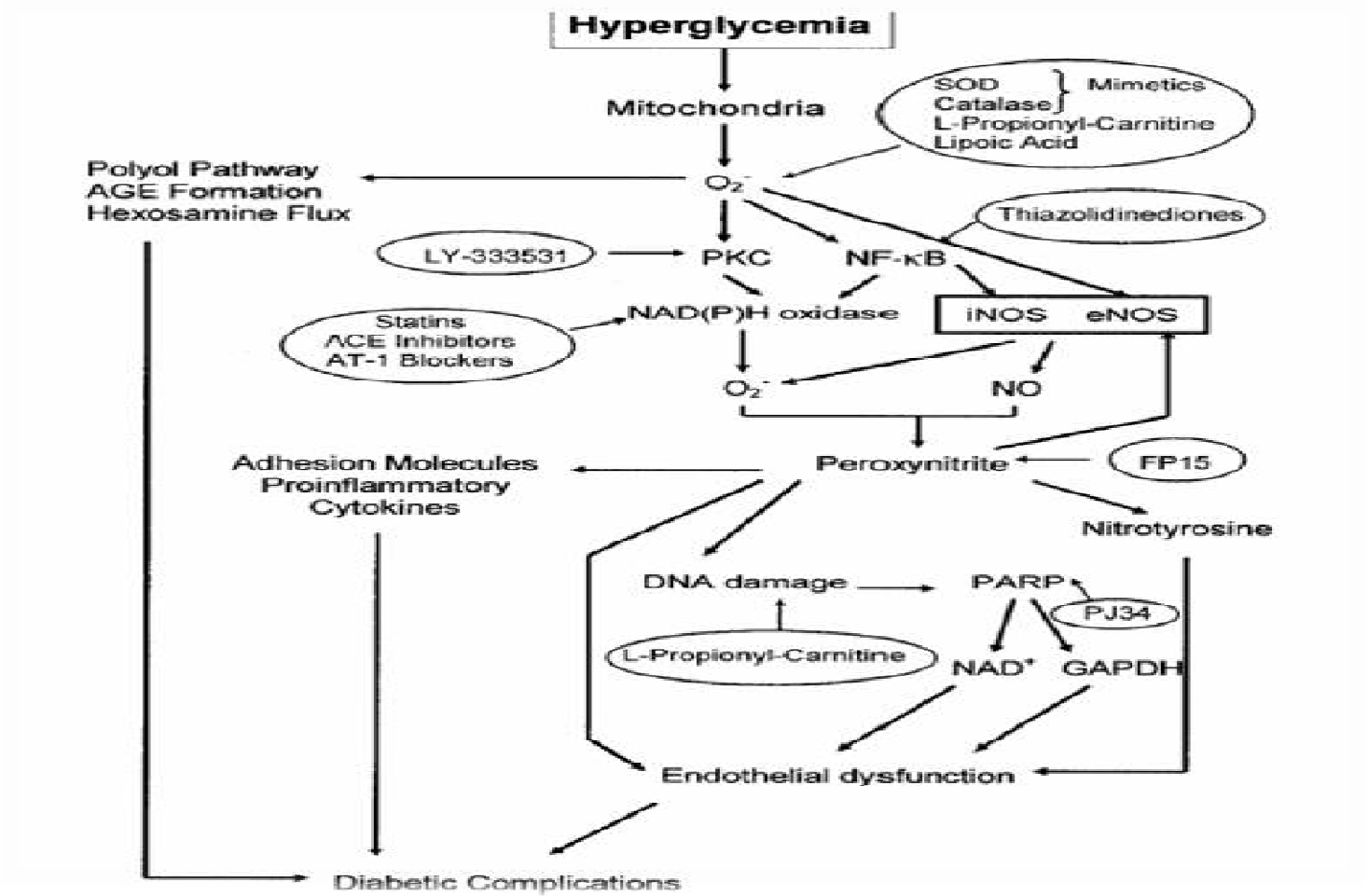
Fasting Plasma Glucose Variability Predicts 10-Year Survival of Type 2 Diabetic Patients

The Verona Diabetes Study

MICHELE MUGGEO, MD
GIACOMO ZOPPINI, MD
ENZO BONORA, MD
ELISABETTA BRUN, MD
RICCARDO C. BONADONNA, MD
PAOLO MOGHETTI, MD
GIUSEPPE VERLATO, MD

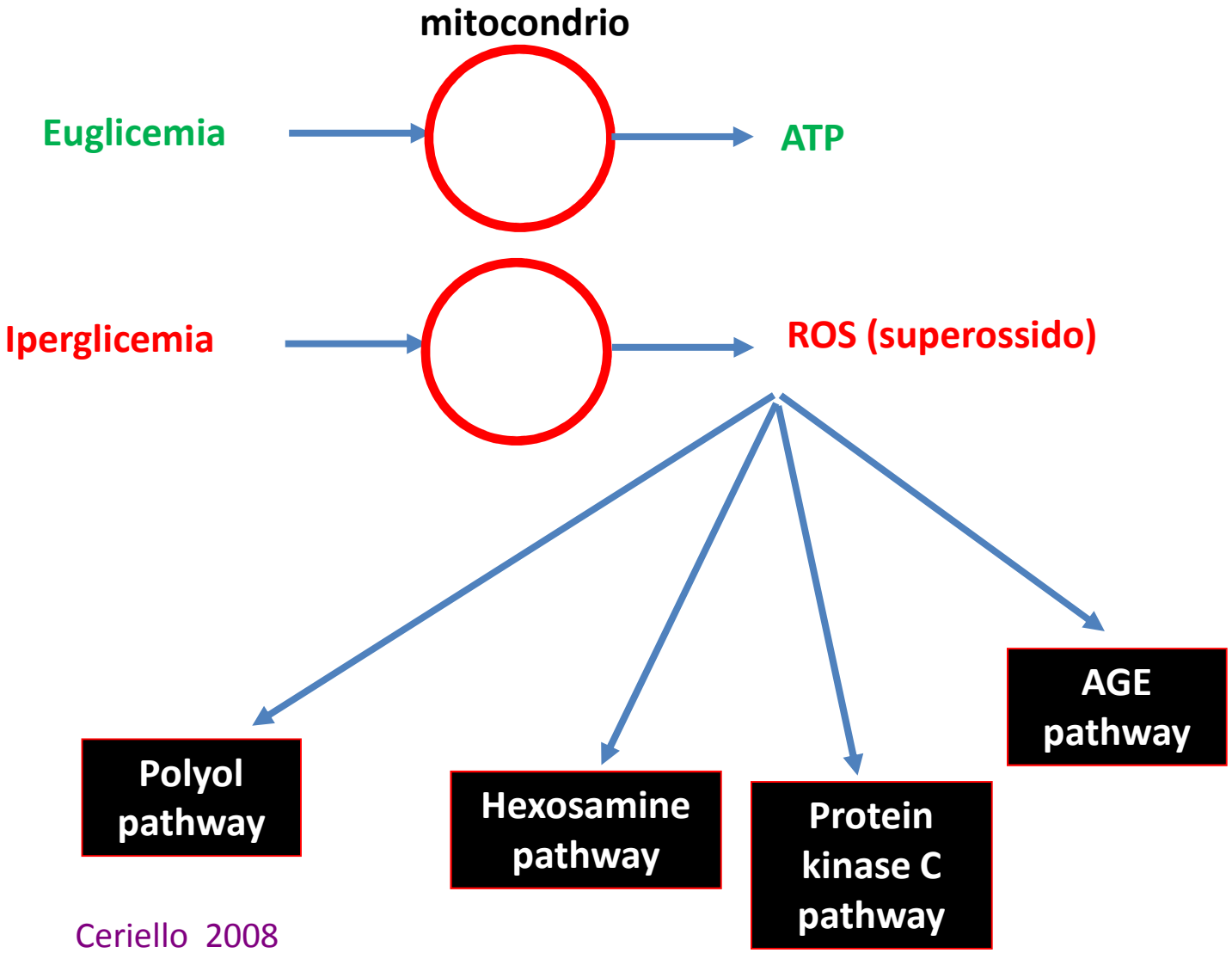
DIABETES CARE, VOLUME 23, NUMBER 1, JANUARY 2000

L’iperglicemia postprandiale aumenta lo stress ossidativo a livello mitocondriale



Ceriello Diabetes Care 2003

Stress ossidativo e complicanze del diabete



Ceriello 2008

0021-972X/06/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 91(3):813–819
Copyright © 2006 by The Endocrine Society
doi: 10.1210/jc.2005-1005

Postprandial Blood Glucose Is a Stronger Predictor of Cardiovascular Events Than Fasting Blood Glucose in Type 2 Diabetes Mellitus, Particularly in Women: Lessons from the San Luigi Gonzaga Diabetes Study

F. Cavalot, A. Petrelli, M. Traversa, K. Bonomo, E. Fiora, M. Conti, G. Anfossi, G. Costa, and M. Trovati

Diabetes Unit, Department of Clinical and Biological Sciences, University of Turin, San Luigi Gonzaga Hospital (F.C., M.Tra., K.B., E.F., M.C., G.A., M.Tro.), and Department of Public Health, University of Turin (A.P., G.C.), 10043 Orbassano, Turin, Italy

Objective: The influence of postprandial blood glucose on diabetes complications is intensively debated. We aimed to evaluate the predictive role of both fasting and postprandial blood glucose on cardiovascular events in type 2 diabetes and the influence of gender.

Methods: In a population of 529 (284 men and 245 women) consecutive type 2 diabetic patients attending our diabetes clinic, we evaluated the relationships, corrected for cardiovascular risk factors and type of treatment, between cardiovascular events in a 5-yr follow-up and baseline values of hemoglobin A1c (HbA1c) and blood glucose measured: 1) after an overnight fast, 2) after breakfast, 3) after lunch, and 4) before dinner. Continuous variables were categorized into tertiles.

Results: We recorded cardiovascular events in 77 subjects: 54 of 284 men (19%) and 23 of 245 women (9.4%). Univariate analysis indicated that cardiovascular events were associated with increasing age, longer diabetes duration, and higher HbA1c and fibrinogen in men, and higher systolic blood pressure, albumin excretion rate, HbA1c, and all blood glucose values in women. Smoking was more frequent in subjects with events. When all blood glucose values and HbA1c were introduced simultaneously in the models, only blood glucose after lunch predicted cardiovascular events, with hazard ratio of the third tertile *vs.* the first and the second tertiles greater in women (5.54; confidence interval, 1.45–21.20) than in men (2.12; confidence interval, 1.04–4.32; $P < 0.01$).

Conclusions: Postprandial, but not fasting, blood glucose is an independent risk factor for cardiovascular events in type 2 diabetes, with a stronger predictive power in women than in men, suggesting that more attention should be paid to postprandial hyperglycemia, particularly in women. (***J Clin Endocrinol Metab* 91: 813–819, 2006**)

San Luigi Gonzaga Diabetes Study

Epidemiology/Health Services Research
ORIGINAL ARTICLE

Postprandial Blood Glucose Predicts Cardiovascular Events and All-Cause Mortality in Type 2 Diabetes in a 14-Year Follow-Up

Lessons from the San Luigi Gonzaga Diabetes Study

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ANDREA PAGLIARINO, PHD
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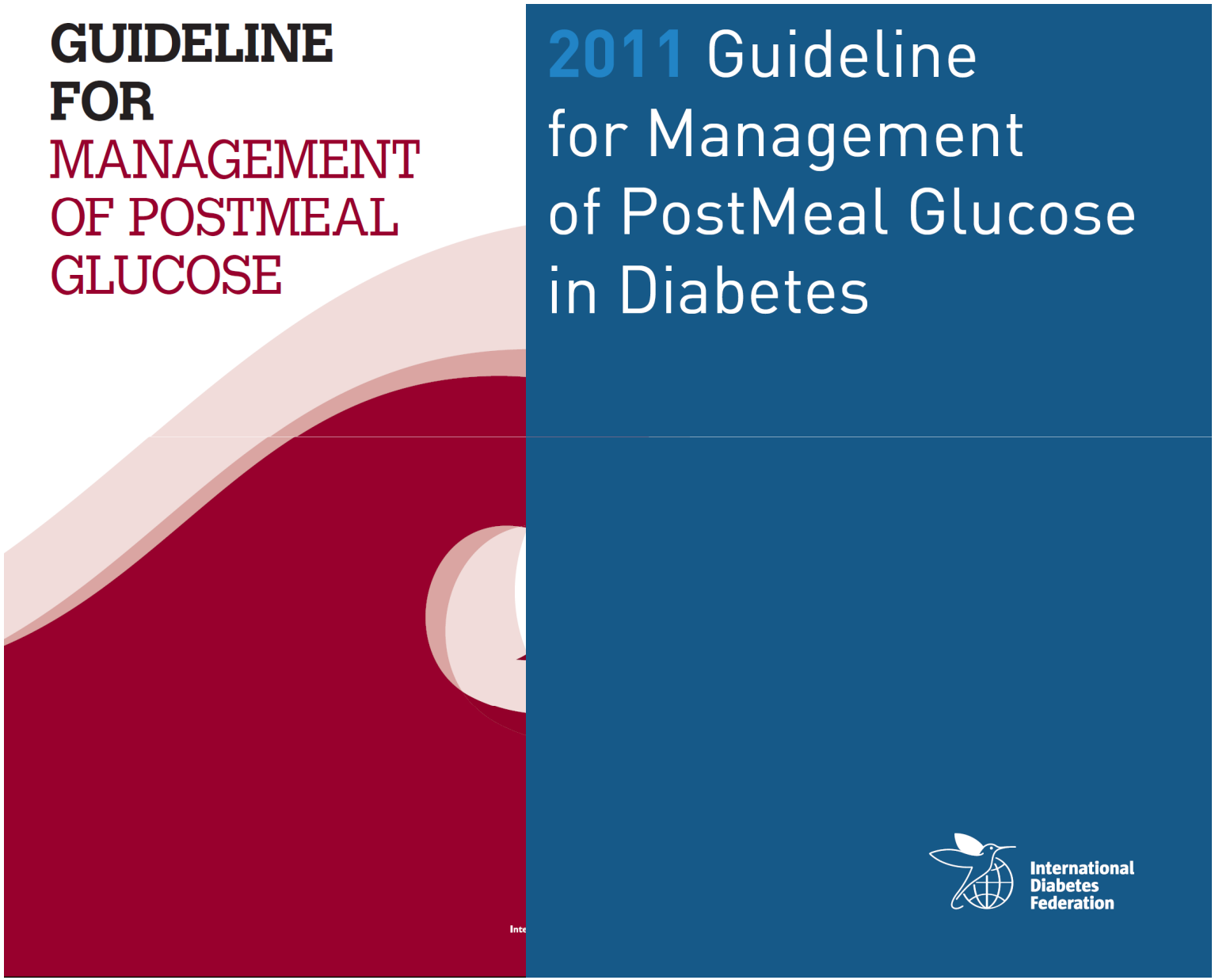
PAOLA MASSUCCO, MD
GIOVANNI ANFOSSI, MD
MARIELLA TROVATI, MD

Diabetes Care 34:2237-2243,2011



Ceriello 2007

Fenotipizzazione del paziente

Patients are "phenotyped" on the basis of:

- HbA1c
- type and prevalence of blood glucose levels during the day, using fasting/pre-prandial glucose levels and those taken 2 hours after main meals with SMBG.

In line with existing recommendations[1-5] target values were fixed at:

- 70-130 mg/dl for fasting/pre-prandial blood glucose
- < 180 mg/dl for post-prandial values.

Analysis of SMBG measurements indicates 2 types of hyperglycaemia:

- *Primarily fasting/pre-prandial*: >60% of fasting/before-meal values indicate hyperglycaemia
- *Primarily post-prandial*: >60% of measurements taken 2 hours after a meal indicate hyperglycaemia

*SMBG: self-monitoring blood glucose

1. Nathan DM, *et al. Diabetes Care* 32(1), 193-203 (2009)
2. AMD-SID. Standard italiani per la cura del diabete mellito 2009-2010
3. www.infodiabetes.it/standard_di_cura/2010_linee_guida.pdf
4. www.siditalia.it/documenti/2010_linee_guida.pdf
5. Duran A, Journal of Diabetes 2 (2010) 203–211.

Gli algoritmi terapeutici di AMD: la personalizzazione terapeutica correlata all'autocontrollo glicemico

DIABETES TECHNOLOGY & THERAPEUTICS
Volume 14, Number 4, 2012
© Mary Ann Liebert, Inc.
DOI: 10.1089/dia.2011.0233

Perspective

Personalizing Treatment in Type 2 Diabetes: A Self-Monitoring of Blood Glucose Inclusive Innovative Approach

Antonio Ceriello, M.D., Ph.D.,[1,2] Marco Gallo, M.D.,[3] Vincenzo Armentano, M.D.,[4] Gabriele Perriello, M.D.,[5] Sandro Gentile, M.D., Ph.D.,[6] and Alberto De Micheli, M.D.,[7]
on behalf of the Associazione Medici Diabetologi

Documento di consenso GdL Terapia Personalizzata AMD Il Giornale di AMD 2011;14:35-45

La personalizzazione della terapia: innovazione nella gestione del paziente con diabete di tipo 2

Ceriello A., Armentano V., De Micheli A., Gallo M., Perriello G., Gentile S.

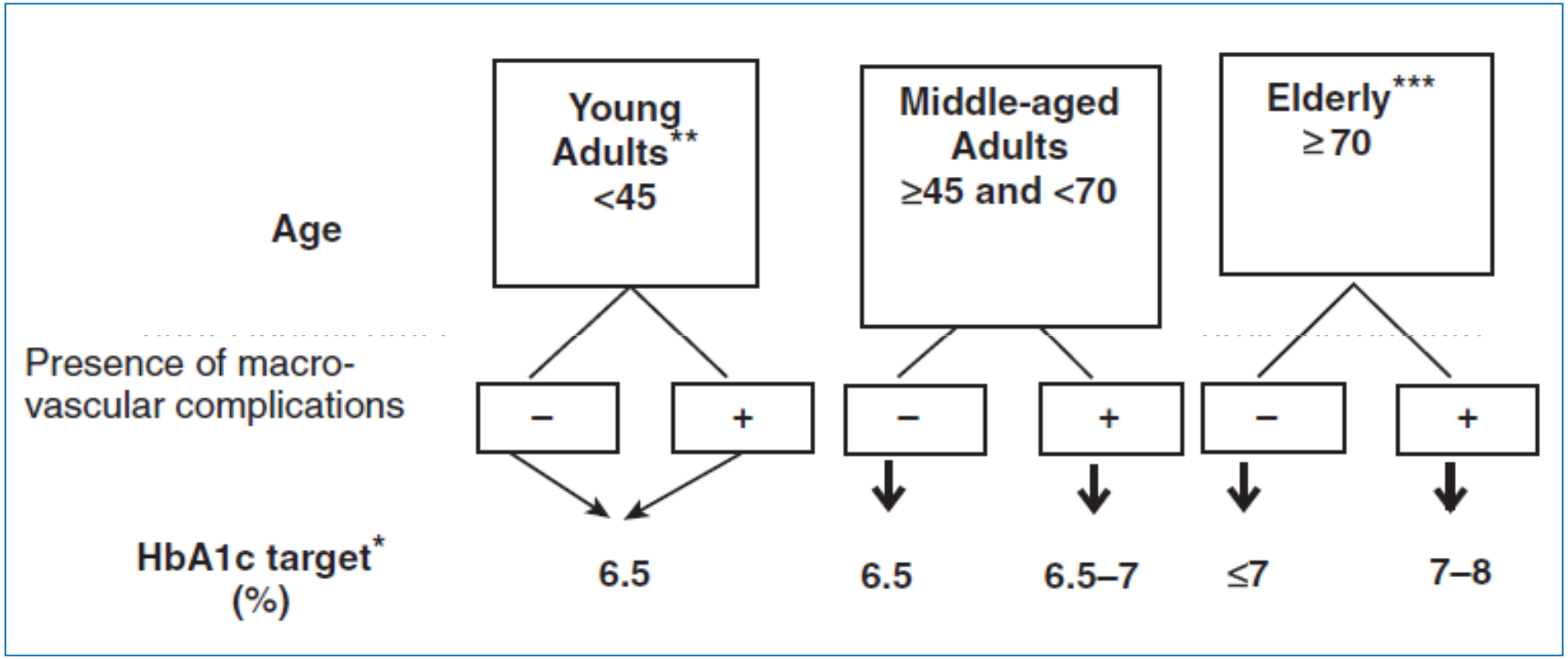
- Caratterizzazione del paziente:
  - situazione clinica generale del paziente
  - entità iperglicemia
  - obesità
  - rischio ipoglicemie
  - insufficienza renale
- Caratterizzazione delle iperglicemie:
  - prevalentemente a digiuno/pre-prandiali
  - prevalentemente post-prandiali
  - pre- e post-prandiali

SMBG quale strumento guida per apportare correzioni più tempestive e ridurre i periodi di iperglicemia

Documento di consenso GdL Terapia Personalizzata AMD Il Giornale di AMD 2011;14:35-45

La personalizzazione della terapia: innovazione nella gestione del paziente con diabete di tipo 2

Ceriello A., Armentano V., De Micheli A., Gallo M., Perriello G., Gentile S.



SMBG quale strumento guida per apportare correzioni più tempestive e ridurre i periodi di iperglicemia

Documento di consenso GdL Terapia Personalizzata AMD Il Giornale di AMD 2011;14:35-45

La personalizzazione della terapia: innovazione nella gestione del paziente con diabete di tipo 2

Terapia Personalizzata

- Con il concetto di terapia personalizzata si intende l'approccio decisionale clinico che di volta in volta viene svolto verso ciascun paziente e che ha come prerequisito un'accurata identificazione del paziente (fenotipizzazione) e, come metodologia, l'applicazione delle conoscenze e delle evidenze scientifiche al buon senso, nonché alla realtà di ciascun individuo
- Il fine ultimo è di ottimizzare le risposte terapeutiche con una migliore tollerabilità e compliance

La personalizzazione della terapia:
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con diabete di tipo 2

Caratterizzazione del paziente

Scegliere la caratteristica principale del paziente con diabete di tipo 2:

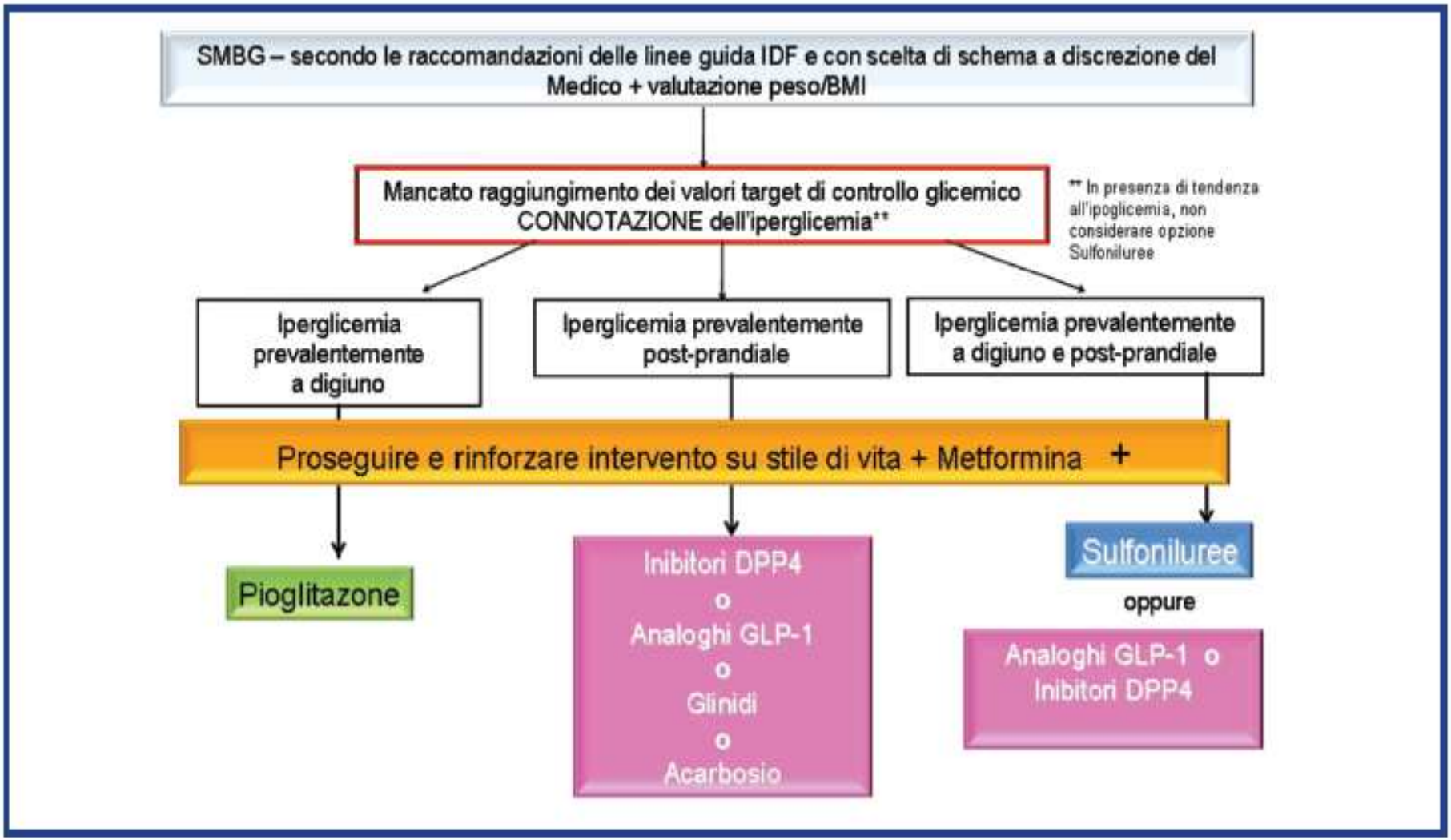
ALGORITMO A	ALGORITMO B	ALGORITMO C	ALGORITMO D	ALGORITMO E	ALGORITMO F
HbA_{1c} ≥75 mmol/mol (≥9%)	BMI <30 e HbA_{1c} 48-75 mmol/mol (tra 6,5 e <9%)	BMI ≥30 e HbA_{1c} 48-75 mmol/mol (tra 6,5 e <9%)	Rischio professionale per possibili ipoglicemie (HbA_{1c} 48-75 mmol/mol [tra 6,5 e <9%])	IRC e HbA_{1c} 48-75 mmol/mol (tra 6,5 e <9%)	Anziano fragile con iperglicemia lieve/moderata (HbA_{1c} <75 mmol/mol [<9%])

SMBG quale strumento guida per apportare correzioni più tempestive e ridurre i periodi di iperglicemia

 Il Giornale di AMD 2011;14:35-45

La personalizzazione della terapia: innovazione nella gestione del paziente con diabete di tipo 2

Ceriello A., Armentano V., De Micheli A., Gallo M., Perriello G., Gentile S.



http://www.aemmedi.it/algoritmi_it_2013/

LA PERSONALIZZAZIONE DELLA TERAPIA NEL DIABETE DI TIPO 2

Versione italiana – ultimo aggiornamento e revisione: maggio 2013

PERSONALISATION OF THERAPY IN TYPE 2 DIABETES

English version – Last update and review: May 2013

M Gallo

Documento di consenso GdL Terapia Personalizzata AMD *Il Giornale di AMD 2011;14:35-45*

La personalizzazione della terapia:
innovazione nella gestione del paziente
con diabete di tipo 2

vantaggi…

- valorizza il ruolo della FPG e PPG
- tiene conto della variabilità glicemica
- web-based (ipertesto…)
- periodico aggiornamento
- condivisa con SIMG, rivolta agli MMG/gestione integrata
- mobile App

La personalizzazione della terapia: innovazione nella gestione del paziente con diabete di tipo 2

Available on the App Store

L'applicazione è riservata **ad un uso professionale, da parte di personale medico,** ed è scaricabile gratuitamente da APP store.

Attivazione della APP e disclaimer

La prima volta che si accede all'**applicazione per iPhone** si devono accettare le modalità di utilizzo del disclaimer, e si deve inserire la password di attivazione.

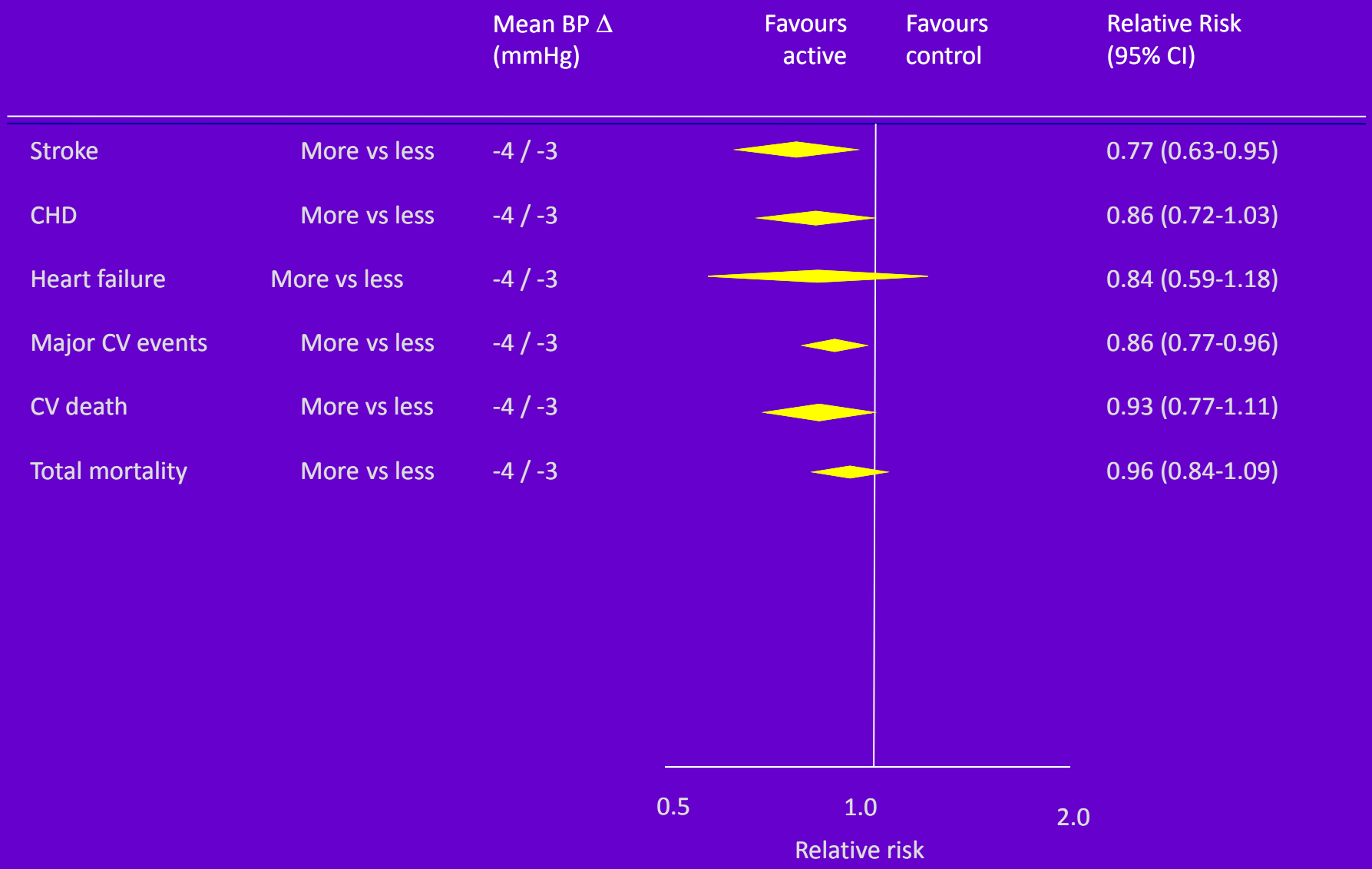
"Compound Target" in Type 2 Diabetes therapy

- To lower HbA_1c levels (early and sustained intensive glycemic control, no therapeutic Inertia)
- To reduce fasting and post-prandial glucose levels

- To reduce CV events and mortality
- To lower the incidence of microvascular disease
- To improve the quality of life
- To preserve β-cell mass (durability)
- To delay progression of disease
- To avoid weight gain
- To meet patient's compliance (administration of drugs, hypoglycemia, etc.)

Personalizzazione della terapia

More vs less strict BP control

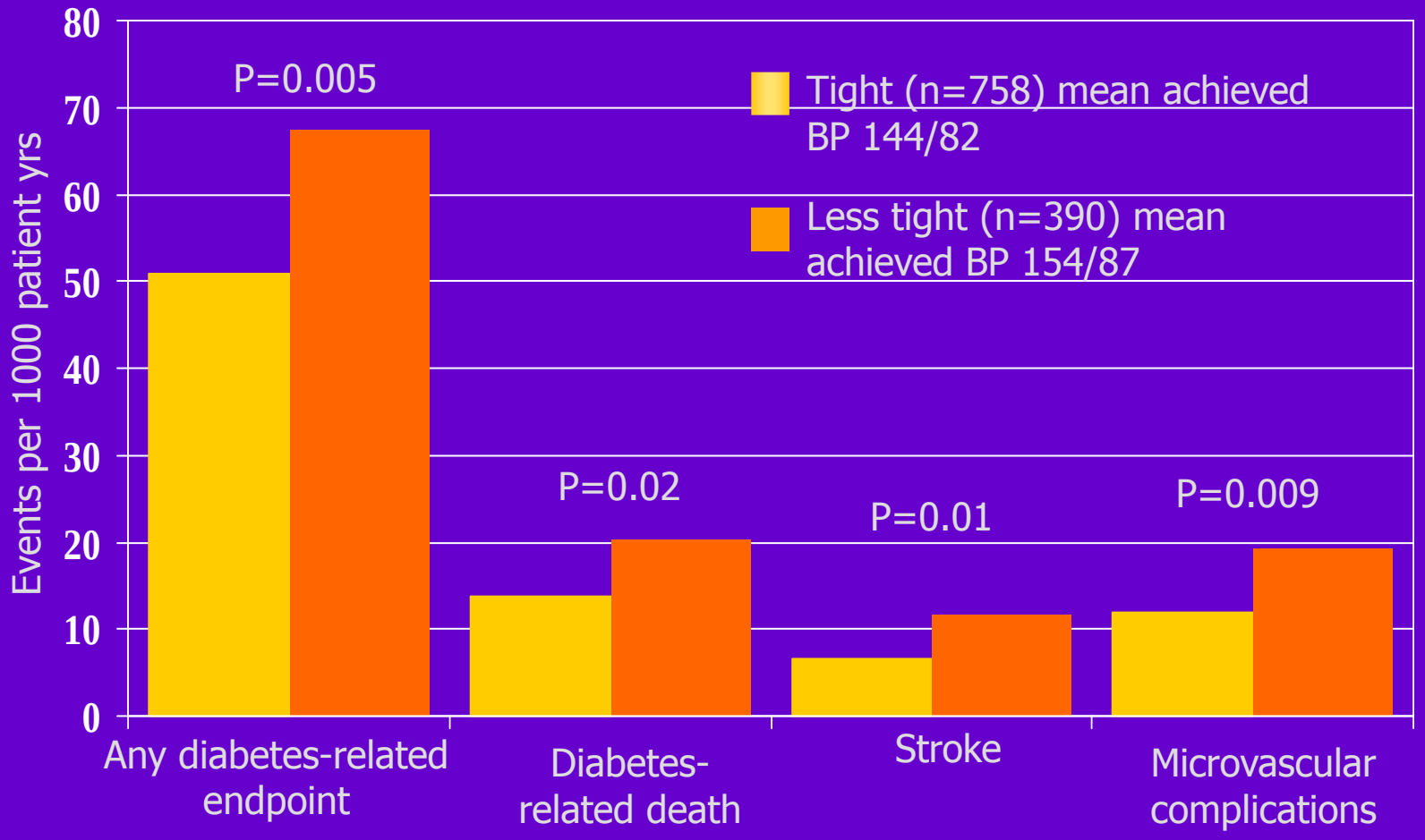


UKPDS:
End-point correlati al diabete tipo 2 e pressione arteriosa

- 12% nel rischio di ogni complicanza associata al diabete
- 15% della mortalità correlata al diabete
- 11% nel rischio di infarto del miocardio
- 13% nel rischio di complicanze microvascolari

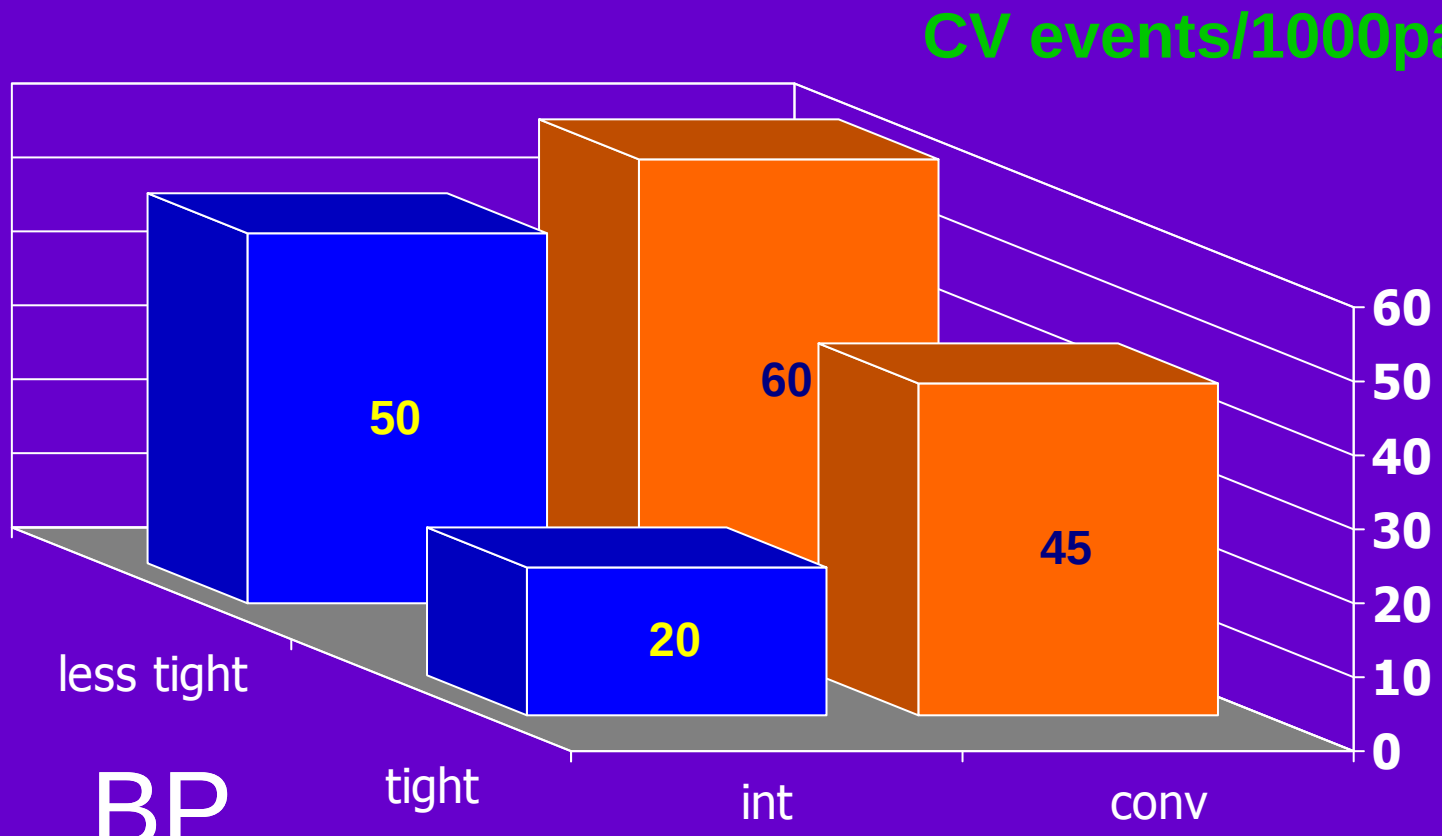
Mod. da Adler AI, et al. for the UKPDS Study Group. BMJ 2000; 321: 412-419.

UKPDS: Blood Pressure



UKPDS, BMJ, 1998

Glucose and Blood Pressure



UKPDS

Tight BP Control in Type 2 Diabetes UKPDS

Population:

1148 patients, mean age 56, mean BP at entry, 160/94

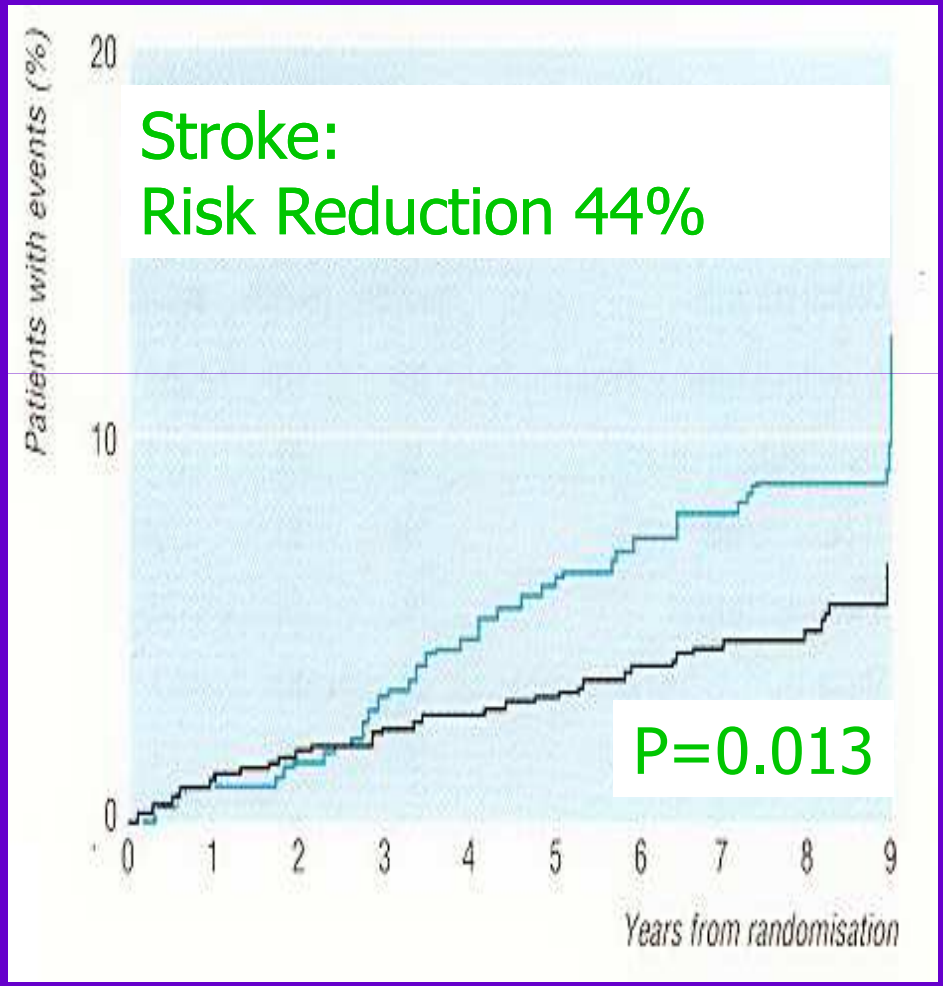
Treatment:

Tight control (aim <150/85) vs less tight (aim <180/105)

Mean BP during follow-up 144/82 vs 154/87 p<0.0001.

Risk reduction:

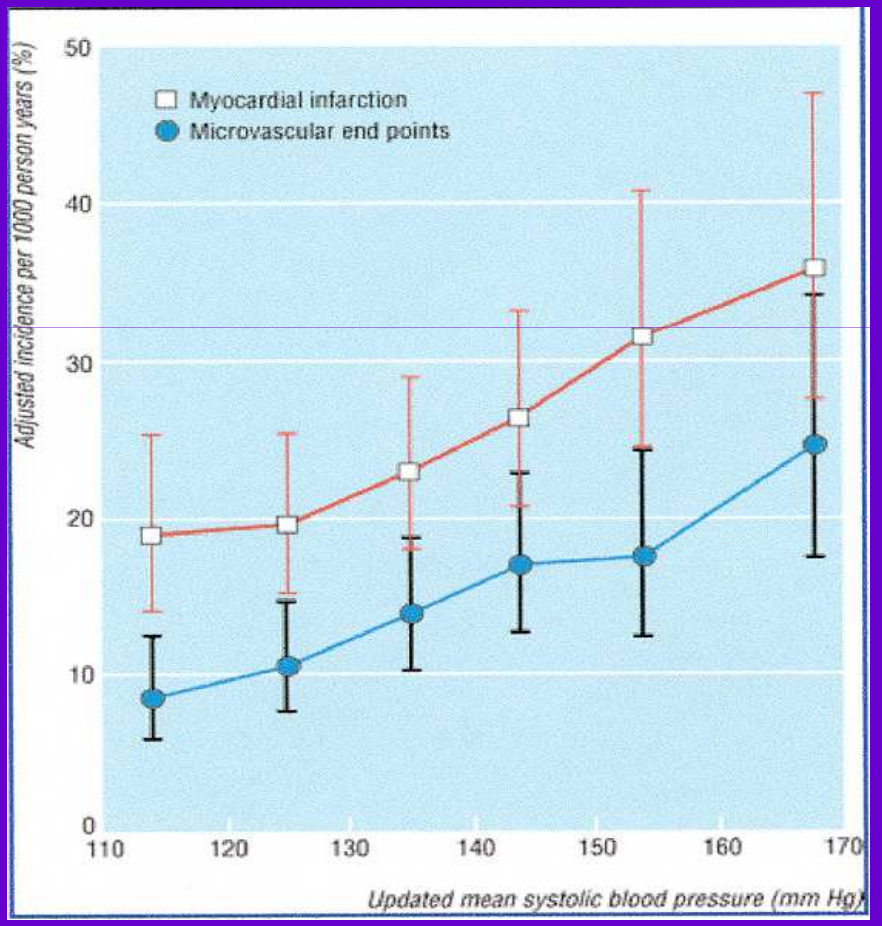
24% diabetes-related endpoints,
32% deaths related to diabetes
37% microvascular end points.



UKPDS, 38 1998

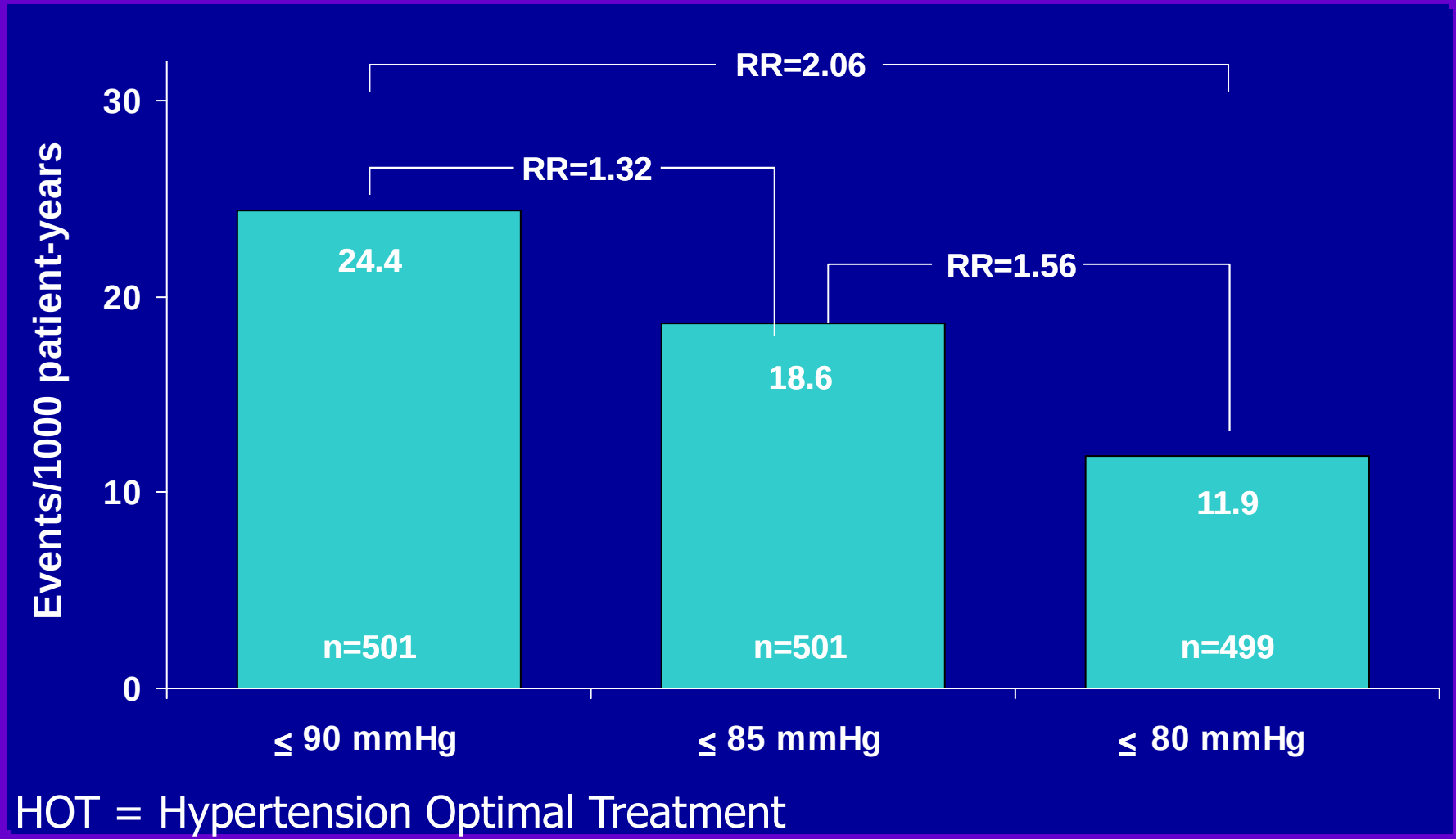
Microvascular end-points, MI and systolic BP

- Incidence rates of microvascular end-points and myocardial infarction by updated mean systolic BP
- Adjusted for age, sex, and ethnic group
- Expressed for white men aged 50-54yrs at Δ and mean diabetes duration 10yrs



Adler et al BMJ 2000

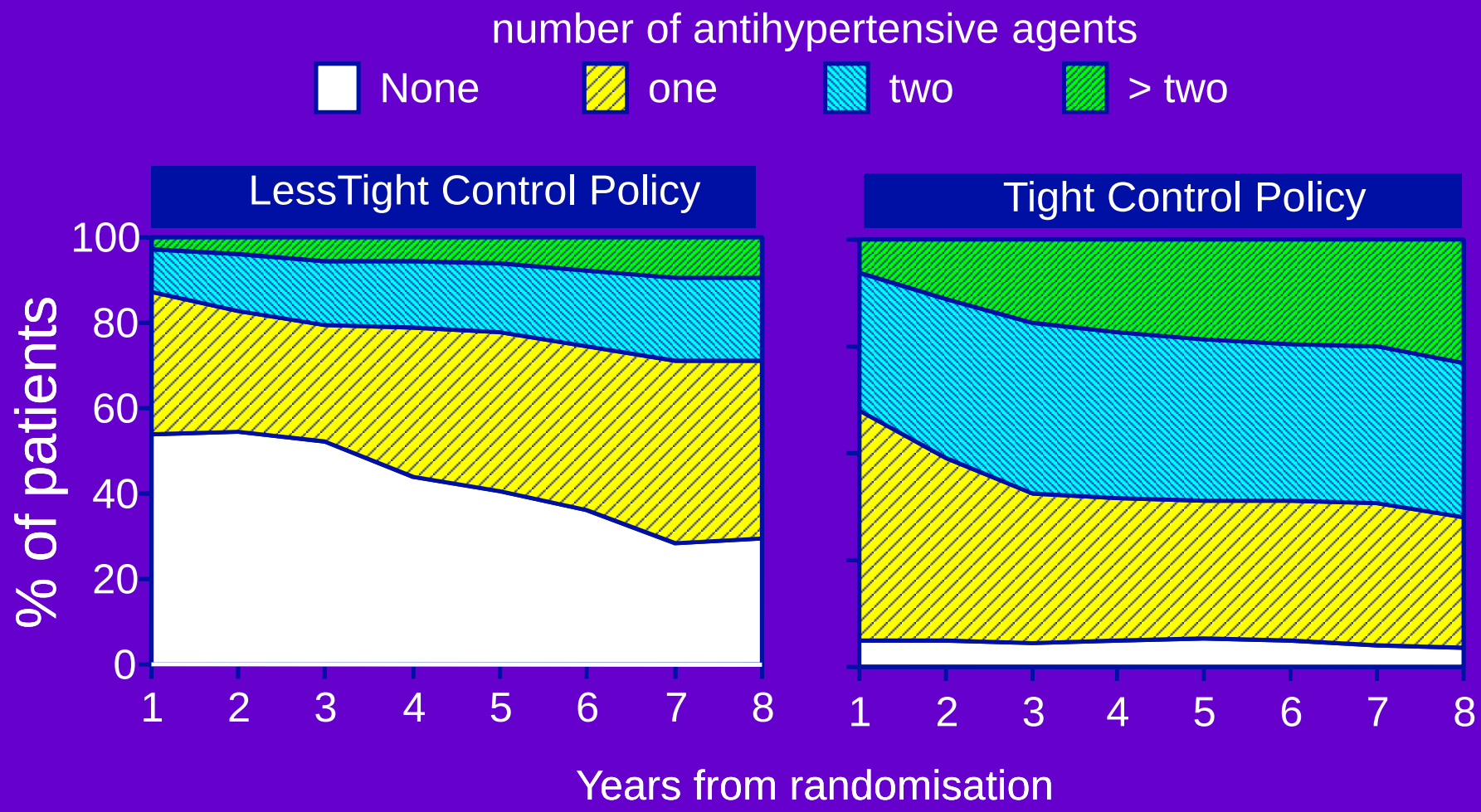
HOT Trial: Major Cardiovascular Events in Patients with Diabetes Mellitus in Relation to Target Blood Pressure Groups



HOT = Hypertension Optimal Treatment

Hansson et al. *Lancet*. 1998;351:1755

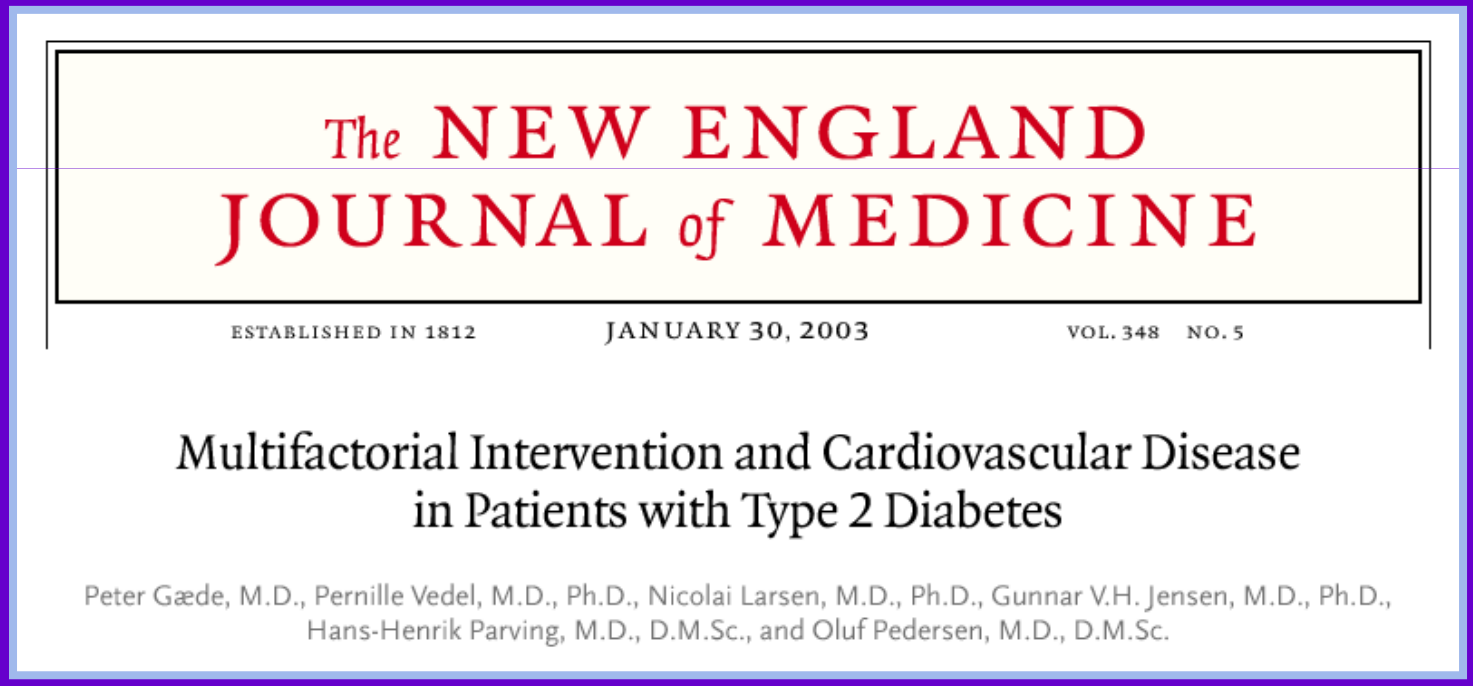
Therapy Requirement



UKPDS

Lo studio Steno-2

L'intervento multifattoriale è efficace per la prevenzione delle malattie CV?



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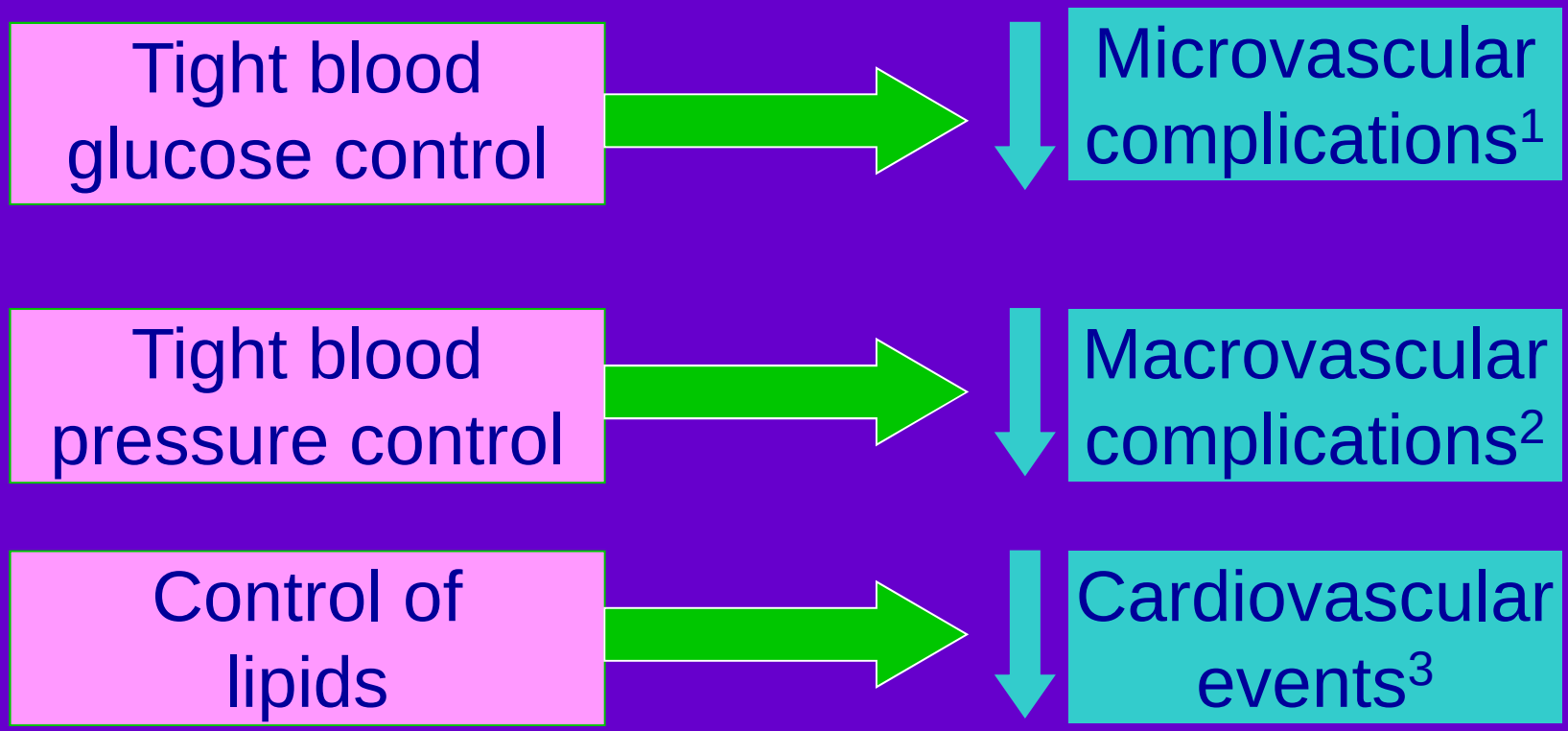
Multifactorial Intervention and Cardiovascular Disease in Patients with Type 2 Diabetes

Peter Gæde, M.D., Pernille Vedel, M.D., Ph.D., Nicolai Larsen, M.D., Ph.D., Gunnar V.H. Jensen, M.D., Ph.D., Hans-Henrik Parving, M.D., D.M.Sc., and Oluf Pedersen, M.D., D.M.Sc.

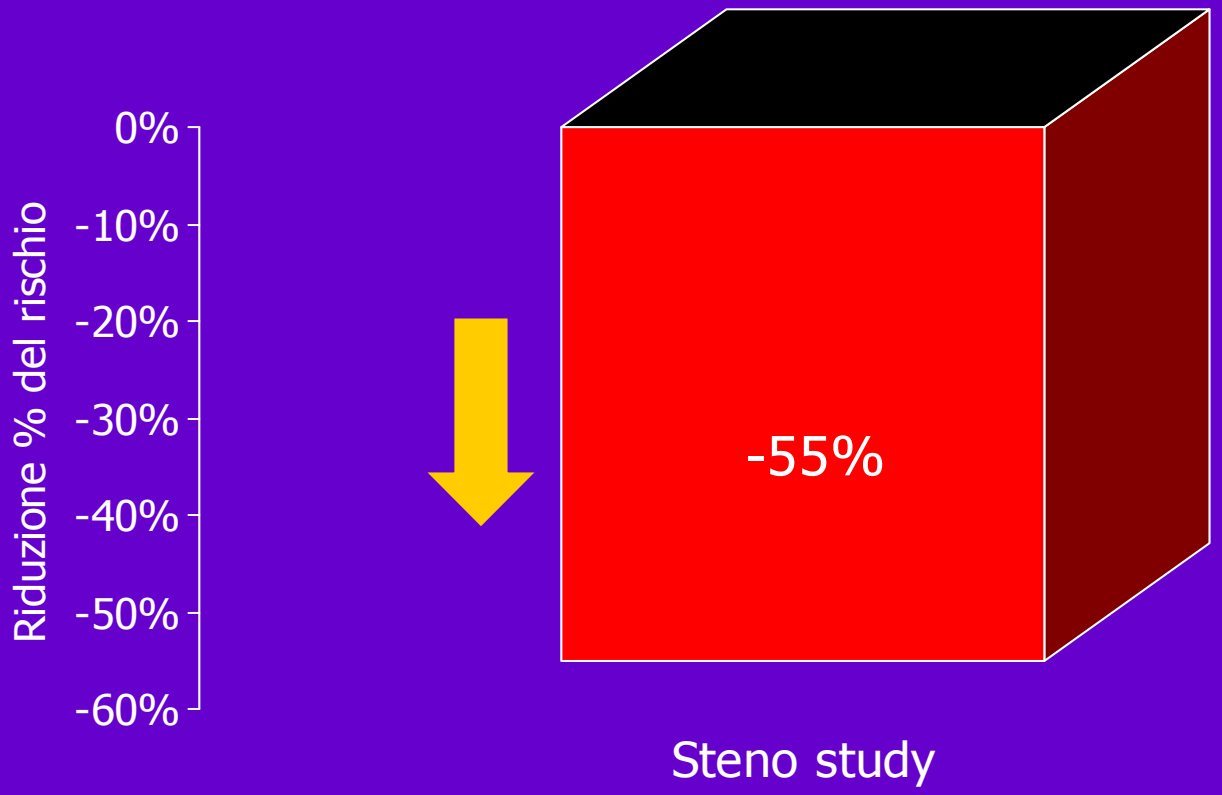
Peter Gæde MD et al., Multifactorial Intervention and Cardiovascular Disease in Patients with Type 2 Diabetes, N Engl J Med 2003;348:383-93

Treatment Targets in Type 2 Diabetes Provide a Basis for Improved Outcomes



1. UKPDS Group. *Lancet* 1998; **352**: 837–53.
2. UKPDS. *BMJ* 1998; **317**: 703–13.
3. Colhoun HM *et al. Lancet* 2004; **364**: 685–96.

Riduzione del rischio cardiovascolare in diabetici : intervento combinato (Gæde P. et al., 1999)



SUMMARY

- Treat early and aggressively (HbA1c < 6.5%), avoiding severe hypoglycaemia
- No legacy from Hypertension, maintain BP at all times on target
- No legacy on Cholesterol, maintain Cholesterol on target
- Treat individuals individually