

ABORDAJE DEL TRATAMIENTO INTENSIVO PRECOZ en **DM2**

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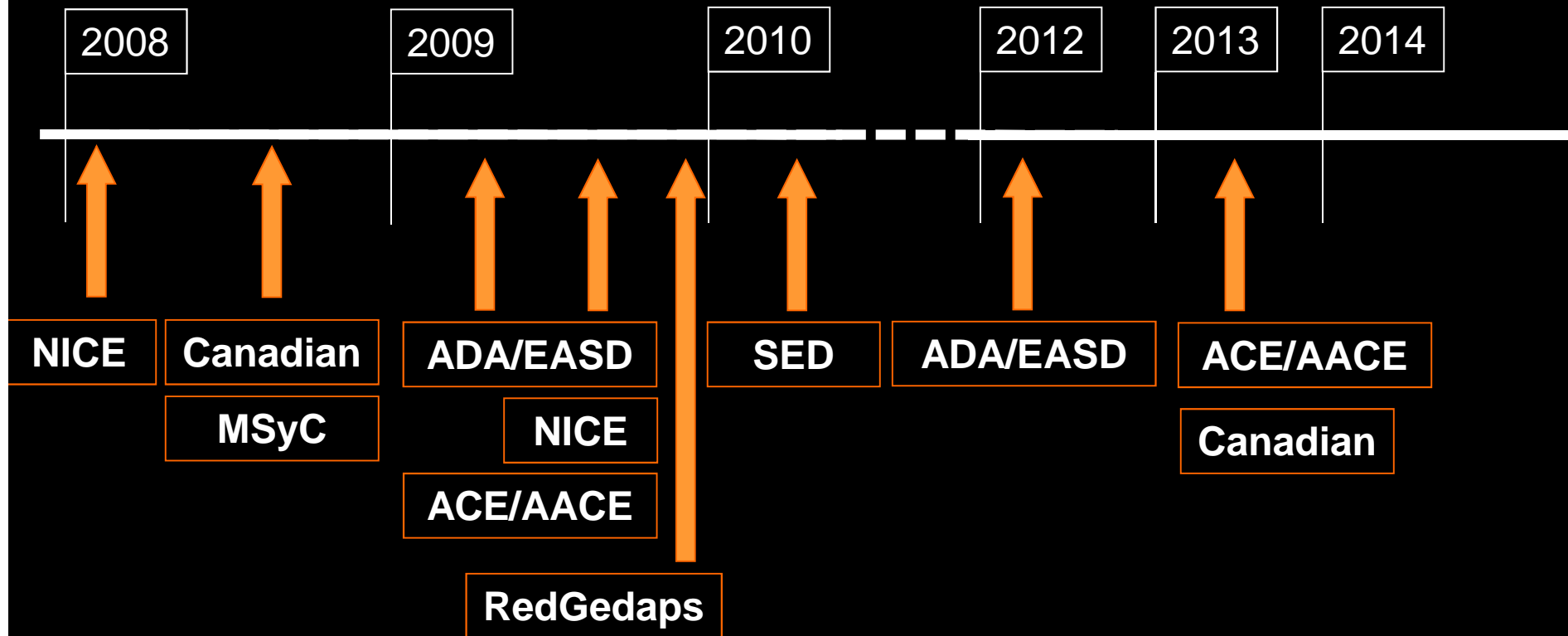
Duality of Interest

- KK: Received funds for research, acted as consultant to or received honoraria from Boehringer Ingelheim, Lilly, MSD, Novartis, Novo Nordisk, Roche, Sanofi-Aventis, Takeda and Unilever.
- XC: Ha recibido honorarios ensayos clínicos, cunsultant y advisory board Boehringer Ingelheim, Lilly, MSD, Abbott, Novartis, Novo Nordisk, Sanofi-Aventis y Astra-Zeneca.

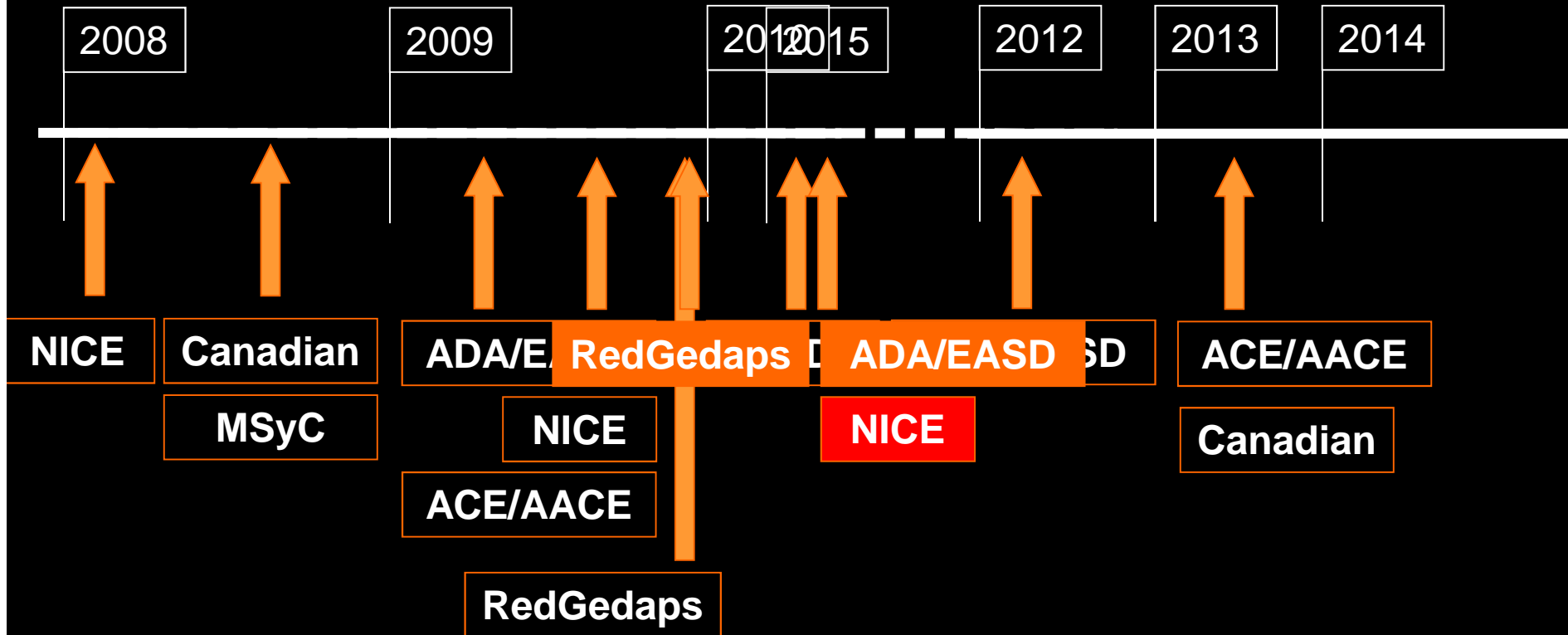
Índice

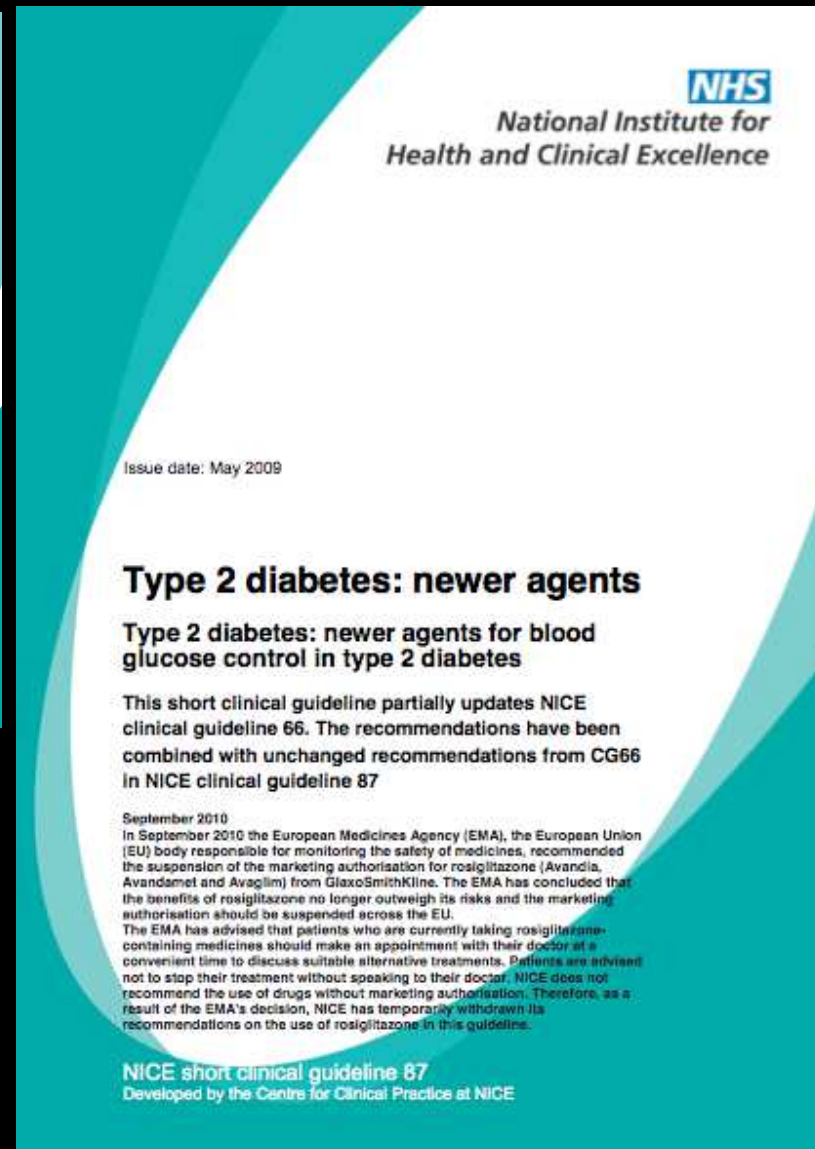
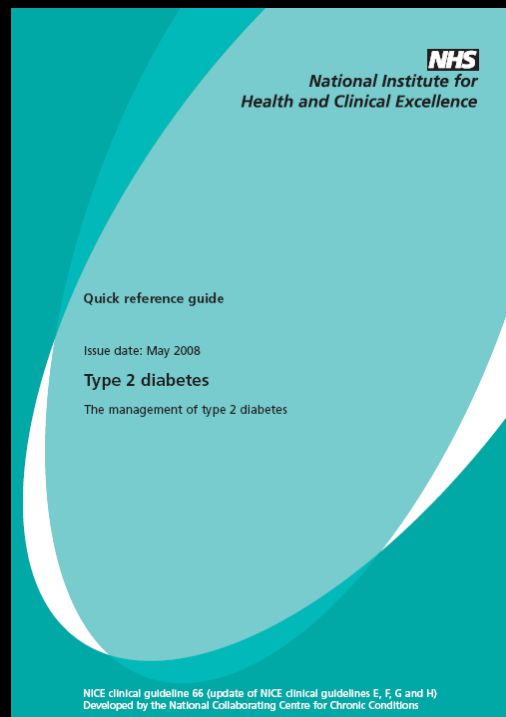
- Guías/recomendaciones Tto. Diabetes
- “La vida real”
- Complejidad de la individualización
- Tratamiento intensivo precoz
- **Take-home** messages

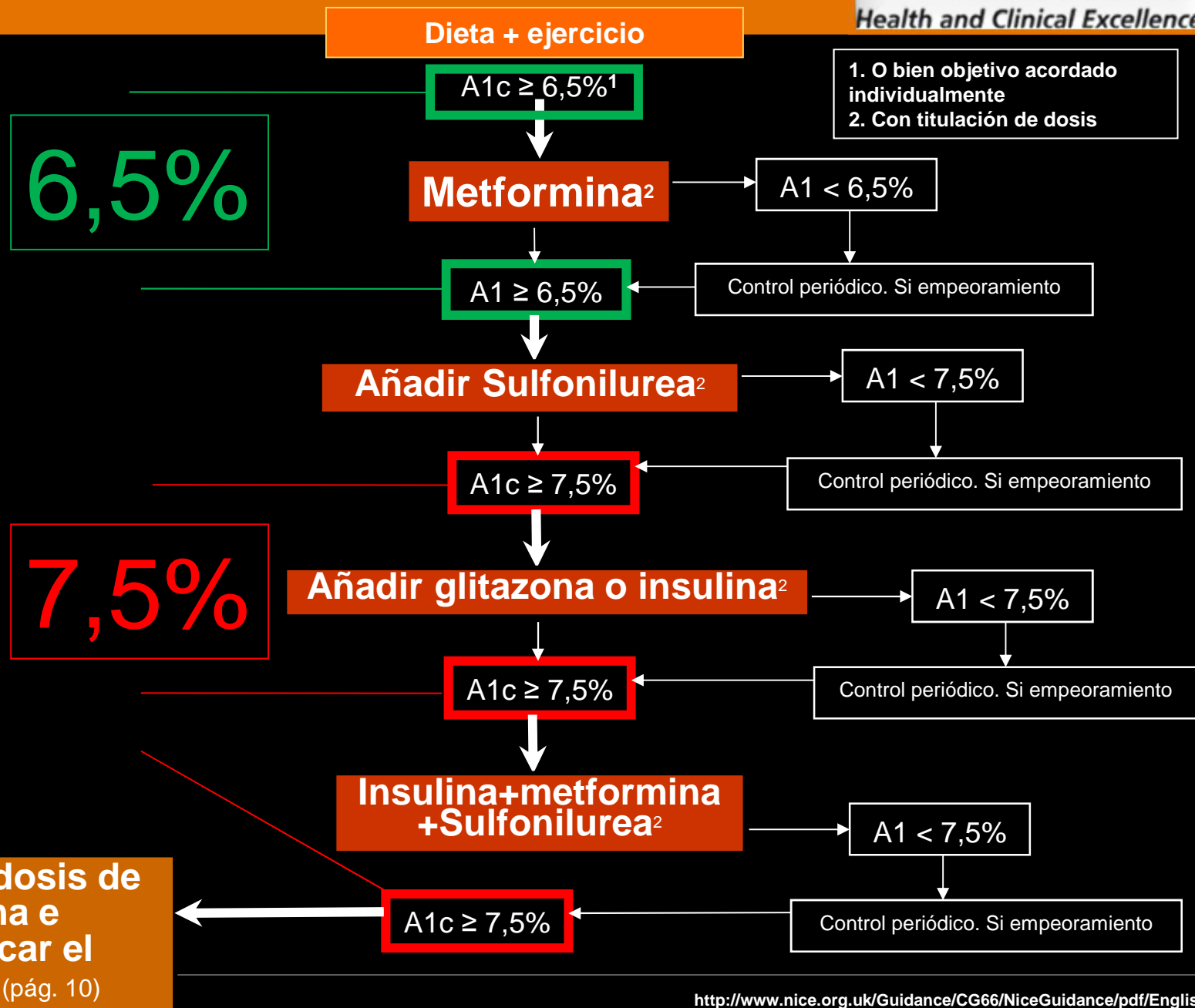
Guías-Recommendaciones



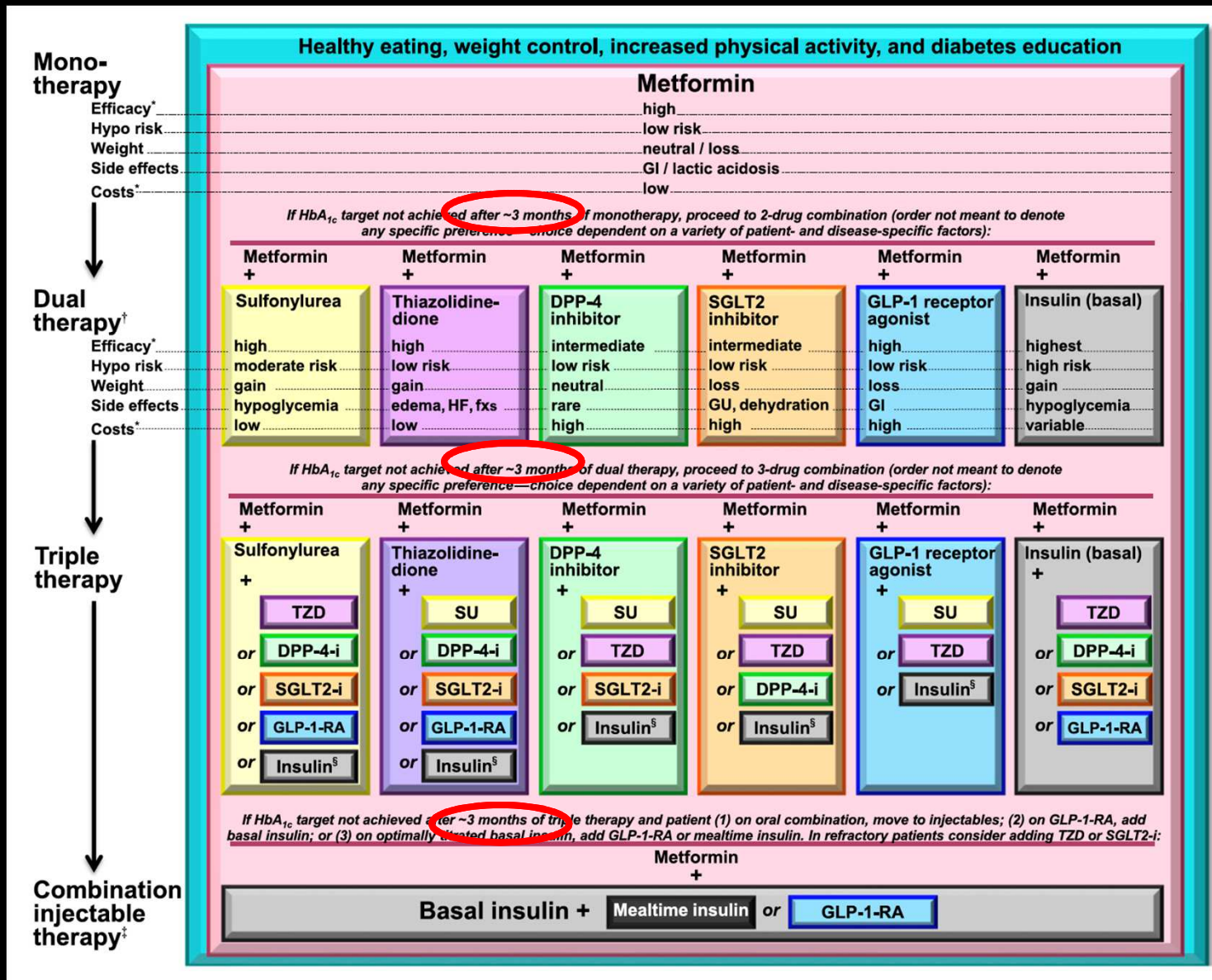
Guías-Recommendaciones

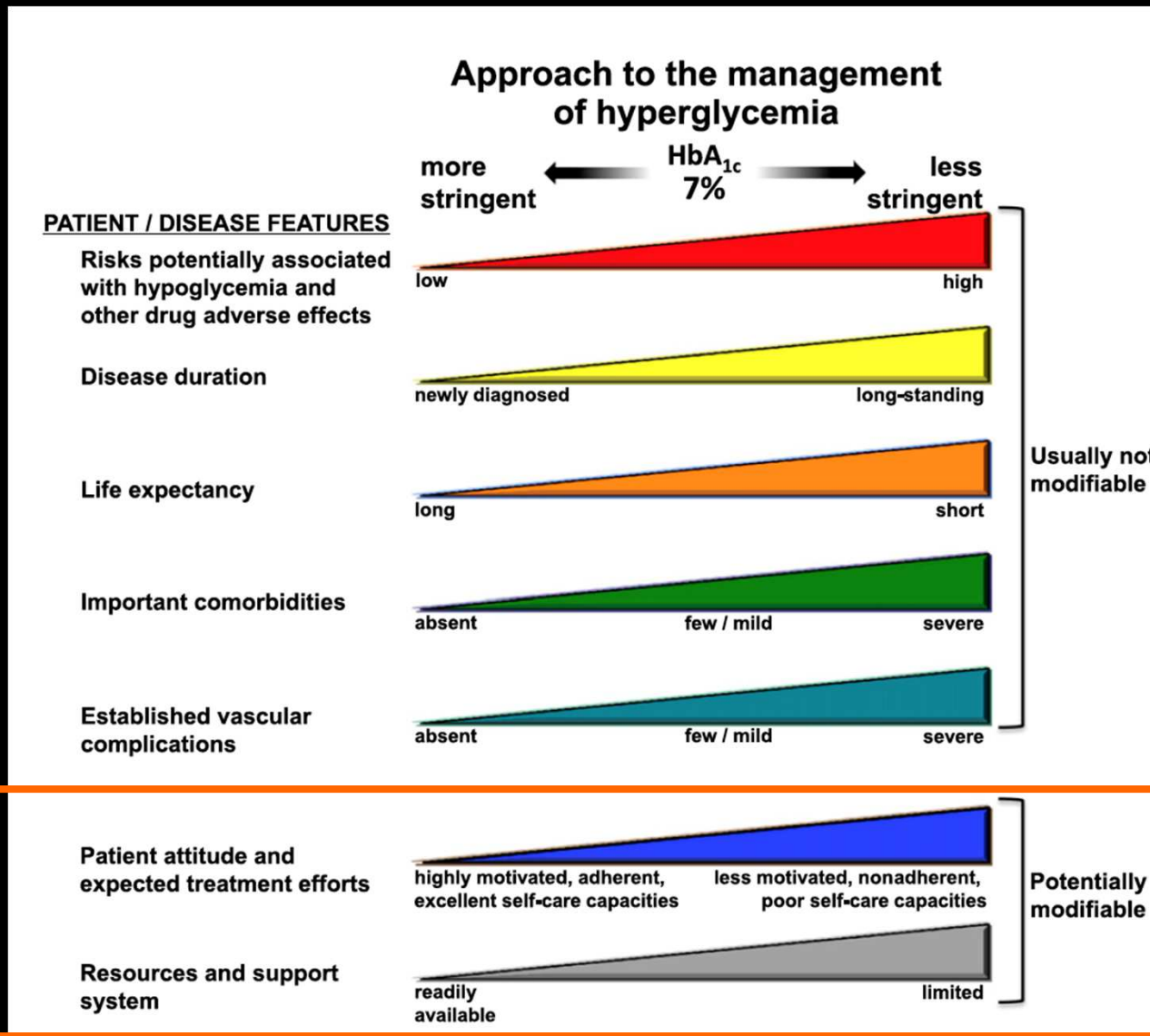






Guías-Recommendaciones





Based on an original figure by Ismail-Beigi et al.

Canadian Diabetes Association Clinical Practice Guidelines

Pharmacologic Management of Type 2 Diabetes

Chapter 13

William Harper, Maureen Clement, Ronald Goldenberg,
Amir Hanna, Andrea Main, Ravi Retnakaran,
Diana Sherifali, Vincent Woo, Jean-François Yale

Clinical Practice Guidelines

Pharmacologic Management of Type 2 Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by William Harper MD, FRCPC, Maureen Clement MD, CCFP, Ronald Goldenberg MD, FRCPC, FACE, Amir Hanna MB, BCh, FRCPC, FACP, Andrea Main BScPhm, CDE, Ravi Retnakaran MD, MSc, FRCPC, Diana Sherifali RN, PhD, CDE, Vincent Woo MD, FRCPC, Jean-François Yale MD, CSPQ, FRCPC



AT DIAGNOSIS OF TYPE 2 DIABETES

Start lifestyle intervention (nutrition therapy and physical activity) +/- Metformin

A1C <8.5%

A1C ≥8.5%

Symptomatic hyperglycemia with metabolic decompensation

If not at glycemic target (2-3 mos)

Start / Increase metformin

Start metformin immediately
Consider initial combination with another antihyperglycemic agent

Initiate insulin +/- metformin

If not at glycemic targets

Add an agent best suited to the individual:

Patient Characteristics

Degree of hyperglycemia
Risk of hypoglycemia
Overweight or obesity
Comorbidities (renal, cardiac, hepatic)
Preferences & access to treatment
Other

Agent Characteristics

BG lowering efficacy and durability
Risk of inducing hypoglycemia
Effect on weight
Contraindications & side-effects
Cost and coverage
Other

See next page...

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From prior page...

Add an agent best suited to the individual (agents listed in alphabetical order):

Class	Relative A1C lowering	Hypo-glycemia	Weight	Other therapeutic considerations	Cost
Alpha-glucosidase inhibitor (acarbose)	↓	Rare	neutral to ↓	Improved postprandial control, GI side effects	\$\$
Incretin agents: DPP-4 Inhibitors	↓↓	Rare	neutral to ↓	GI side effects	\$\$\$
GLP-1 receptor agonists	↓↓ to ↓↓↓	Rare	↓↓		\$\$\$\$
Insulin	↓↓↓	Yes	↑↑	No dose ceiling, flexible regimens	\$-\$\$\$\$
Insulin secretagogue: Meglitinide	↓↓	Yes	↑	Less hypoglycemia in context of missed meals but usually requires TID to QID dosing	\$\$
Sulfonylurea	↓↓	Yes	↑	Gliclazide and glimepiride associated with less hypoglycemia than glyburide	\$
TZD	↓↓	Rare	↑↑	CHF, edema, fractures, rare bladder cancer (pioglitazone), cardiovascular controversy (rosiglitazone), 6-12 weeks required for maximal effect	\$\$
Weight loss agent (orlistat)	↓	None	↓	GI side effects	\$\$\$

If not at glycemic target

- Add another agent from a different class
- Add/Intensify insulin regimen

2013

Make timely adjustments to attain target A1C within 3-6 months

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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*

- GLP-1 RA ✓
- TZD !
- ** SGLT-2 !
- Basal insulin !
- DPP4-i ✓
- Colesevelam ✓
- Bromocriptine QR ✓
- AG-i ✓
- SU/GLN !

2ND LINE AGENT
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

* Order of medications listed are a suggested hierarchy of usage

** Based upon phase 3 clinical trials data

LEGEND

✓ = Few adverse events or possible benefits ! = Use with caution

PROGRESSION OF DISEASE →

Autores

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Documento de consenso

Recomendaciones para el tratamiento farmacológico de la hiperglucemia en la diabetes tipo 2

*Recommendations for the pharmacologic
treatment of hyperglycemia in type 2 diabetes*

Aten Primaria. 2011 Apr;43(4):202.e1-202.e9. Epub 2011 Mar 5.

[Recommendations for the pharmacological treatment of hyperglycemia in type 2 diabetes.]

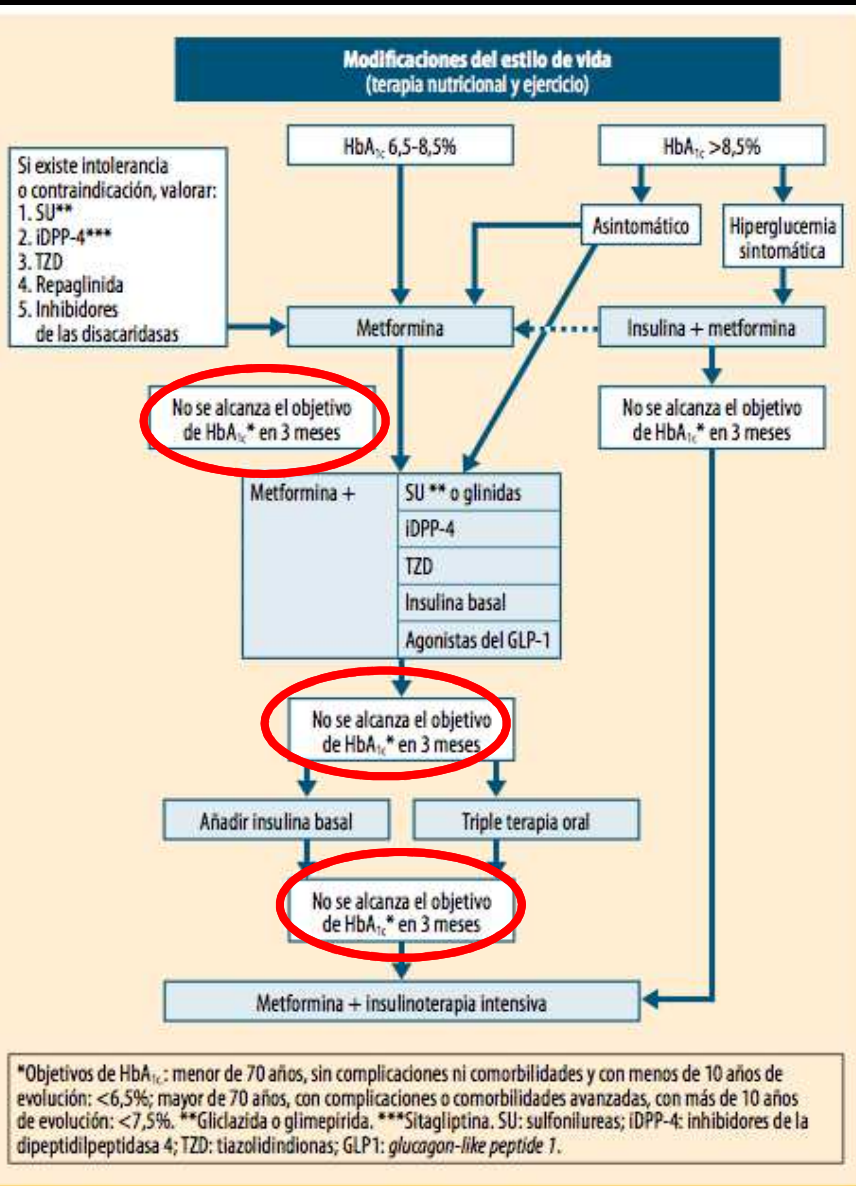
[Article in Spanish]

Menéndez Torre E, Lafita Tejedor FJ, Artola Menéndez S, Millán Núñez-Cortés J, Alonso García A, Puig Domingo M, García Solans JR,

En representación del Grupo de Trabajo de Consensos y Guías Clínicas de la Sociedad Española de Diabetes, España.

PMID: 21382648 [PubMed - as supplied by publisher] **Free Article**

Guías-Recomendaciones



Criterios mayores de Insulinización

- Hiperglucemia severa
- Cetosis
- Pérdida de peso
- Embarazo

↓ A1c > 7%

Metformina

↓ A1c > 7%

Añadir Sulfonilurea*
o glitazona, o glinida, o inhibidor
DPP-4, o inhibidor α -
glucosidasa

Nuevo Algoritmo RedGDPS 2014

Añadir insulina basal
o tercer fármaco oral o agonista
GLP-1*

↓ A1c > 7%

Insulina en
monoterapia
(dos o más
inyecciones)

→ A1c > 7%

Metformina
+ insulina
(dos o más
inyecciones)

El objetivo de A1c < 7% (o < 53 mmol/mol) se debe individualizar según las características del paciente.

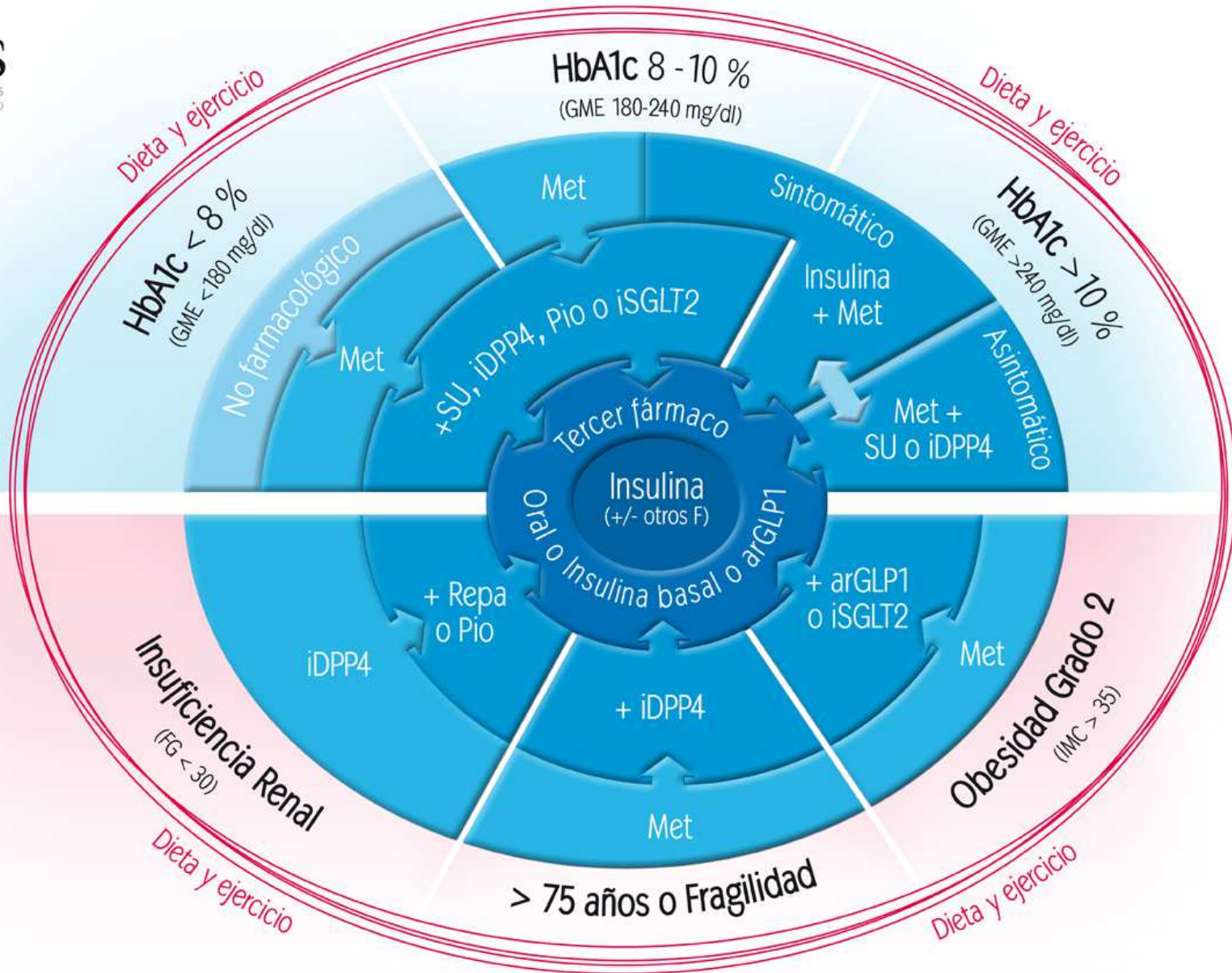
* El segundo o tercer fármaco oral se elegirá en función de las características del paciente y las ventajas e inconvenientes de cada fármaco. En algunos casos se puede optar por añadir insulina basal en el segundo escalón. Ocasionalmente, como alternativa a la insulinización, puede utilizarse un agonista de GLP1 en asociación con metformina y/o sulfonilurea si IMC > 30 kg/m² (35 según la guía NICE 2008)



redGDPS
Red de Grupos de Estudio de la Diabetes
EN ATENCIÓN PRIMARIA DE LA SALUD

GRADO DE CONTROL GLUCÉMICO

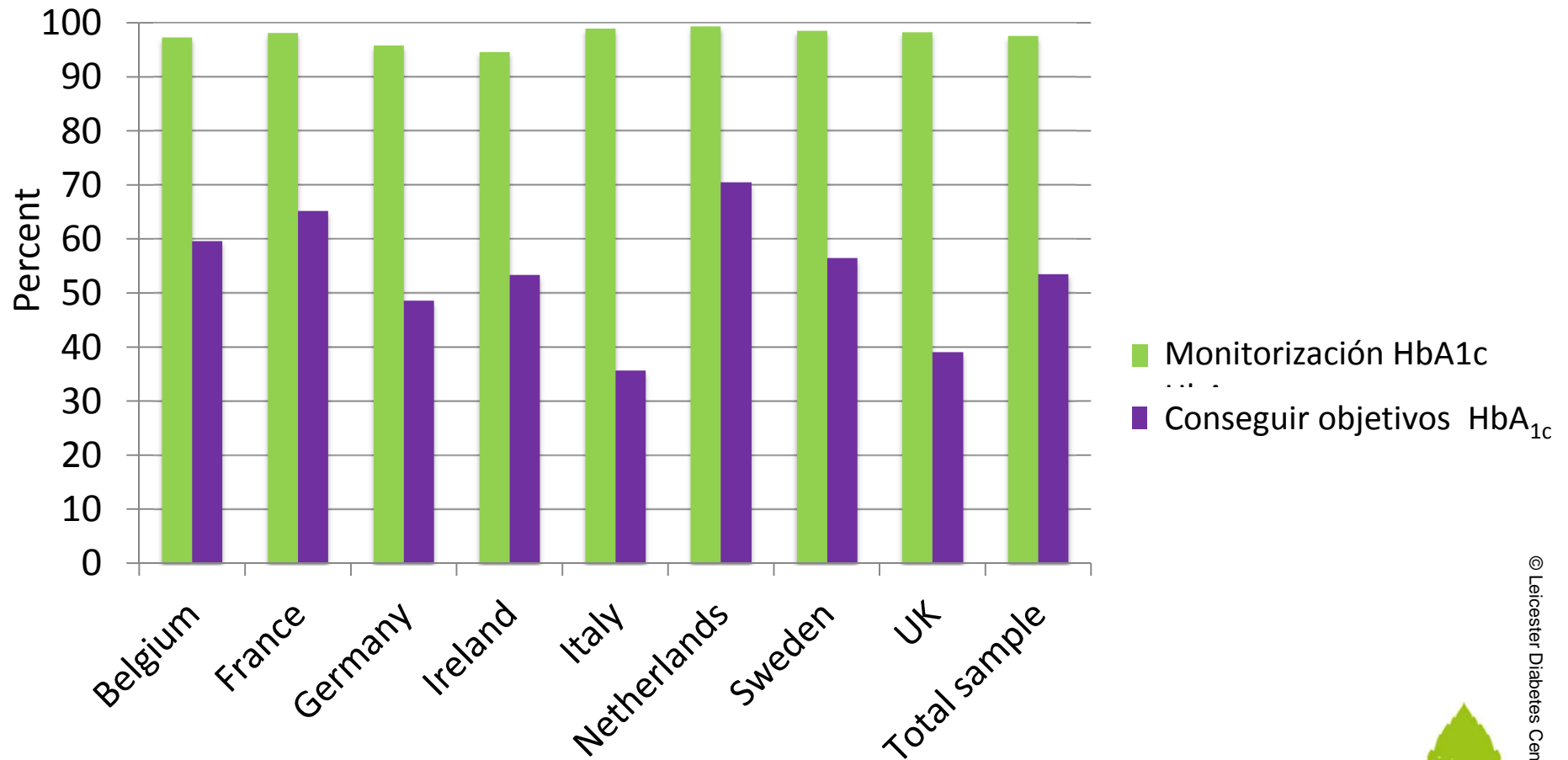
CONDICIONANTE CLÍNICO PREDOMINANTE



A pesar de los avances terapéuticos, una proporción significativa de pacientes DM2 no alcanzan los objetivos de A1c

GUIDANCE Study 7,597 pacientes con T2DM

Existe un vacío entre monitorización y control de la HbA_{1c} <7%



Control of Glycemia and Cardiovascular Risk Factors in Patients With Type 2 Diabetes in Primary Care in Catalonia (Spain)

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DIDAC MAURICIO, MD, PHD^{8,9}

Many studies have shown that the occurrence of these complications depends largely on the degree of glycemic control and intensive control of cardiovascular risk factors (CVRFs) (3–5).

In the last few decades, a consensus

N 286.791 pacientes diabéticos

H 153.987 M 132.804

Edad 68.2

A1c 7.15 % (1.46)

Tiempo Dx 6.5 años

IMC 29.6 kg /m² (5.0)

HTA 77.8 %

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Many studies have shown that the occurrence of these complications depends largely on the degree of glycemic control and intensive control of cardiovascular risk factors (CVRFs) (3–5).
 In the last few decades, a consensus

		Age <65		Age ≥65	
		years	years	years	years
	women = 102,063; ≥65 years = 139,161)			3	58.5
				2	82.5
					3.3
A1C ≤7%	(242,842; women = 114,493; ≥65 years = 159,838)	51.8	58.5	3	30.9
A1C ≤8%	(,623; women = 91,627; ≥65 years = 126,014)	74.2	82.5	5	61.9
A1C >10%	(199,586; women = 95,426; ≥65 years = 130,529)	8	3.3	3	40.6
				2	75.2
				2	35.4
Secondary prevention: A1C ≤7%, BP ≤130/80 mmHg, and LDL-C <100 mg/dL (n = 34,310; women = 12,200; ≥65 years = 27,386)		11.9	12.1	5	42.1
Primary prevention: A1C ≤7%, BP ≤130/80 mmHg, and LDL-C <130 mg/dL (n = 145,605; women = 71,246; ≥65 years = 91,689)		12.9	13.3	12.7	12.2
Secondary prevention: A1C ≤7%, BP ≤130/80 mmHg, and LDL-C <100 mg/dL (n = 34,310; women = 12,200; ≥65 years = 27,386)		12.1	13.3	9.9	11.9
					12.1

Data are percentages. The primary and secondary prevention treatment goals were defined according to the local guidelines. The percentages are from the study subjects with available data for each variable. All variables showed significant differences between sex ($P < 0.005$) and age groups ($P < 0.001$).



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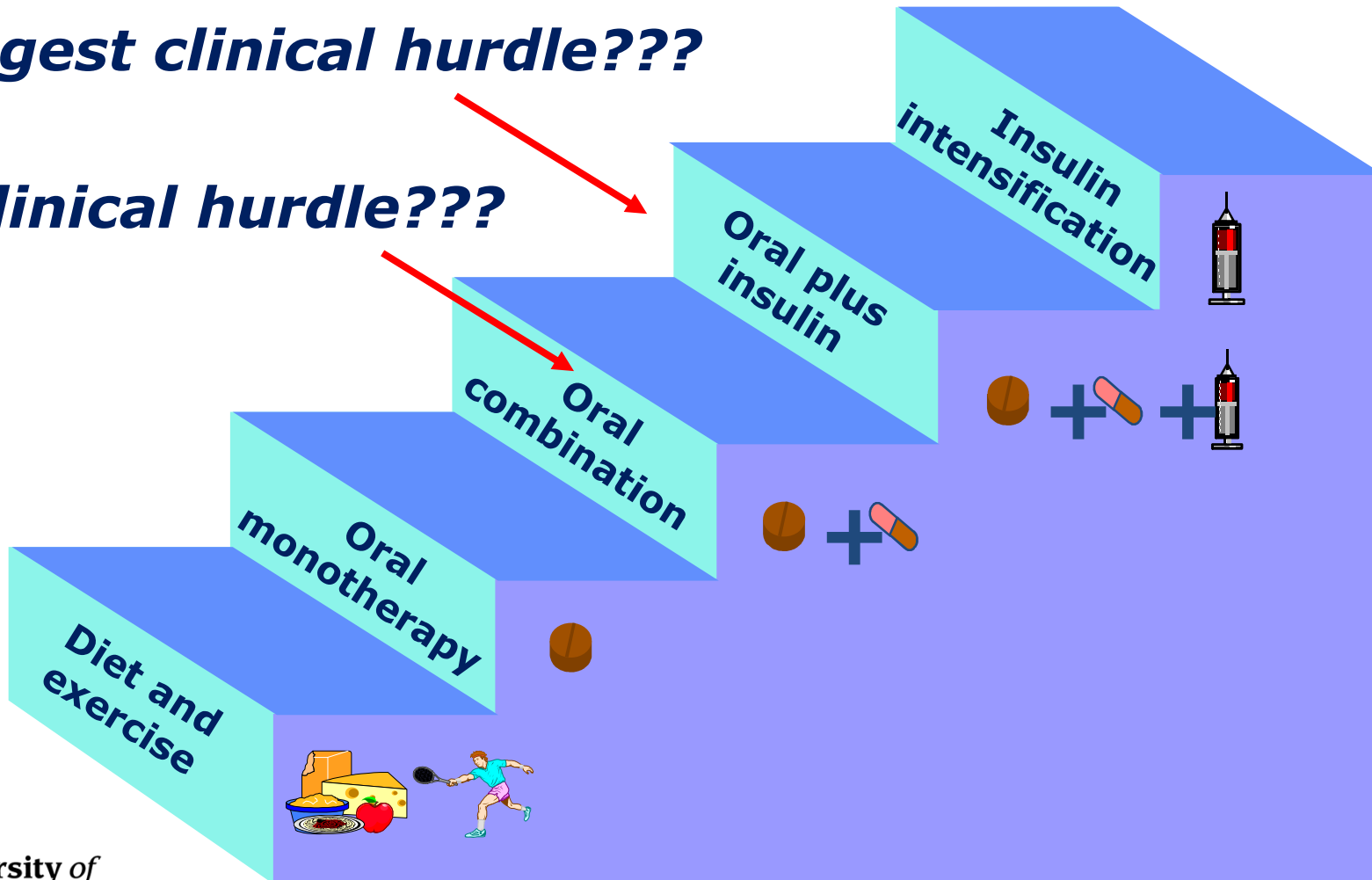


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Stepwise management of type 2 diabetes

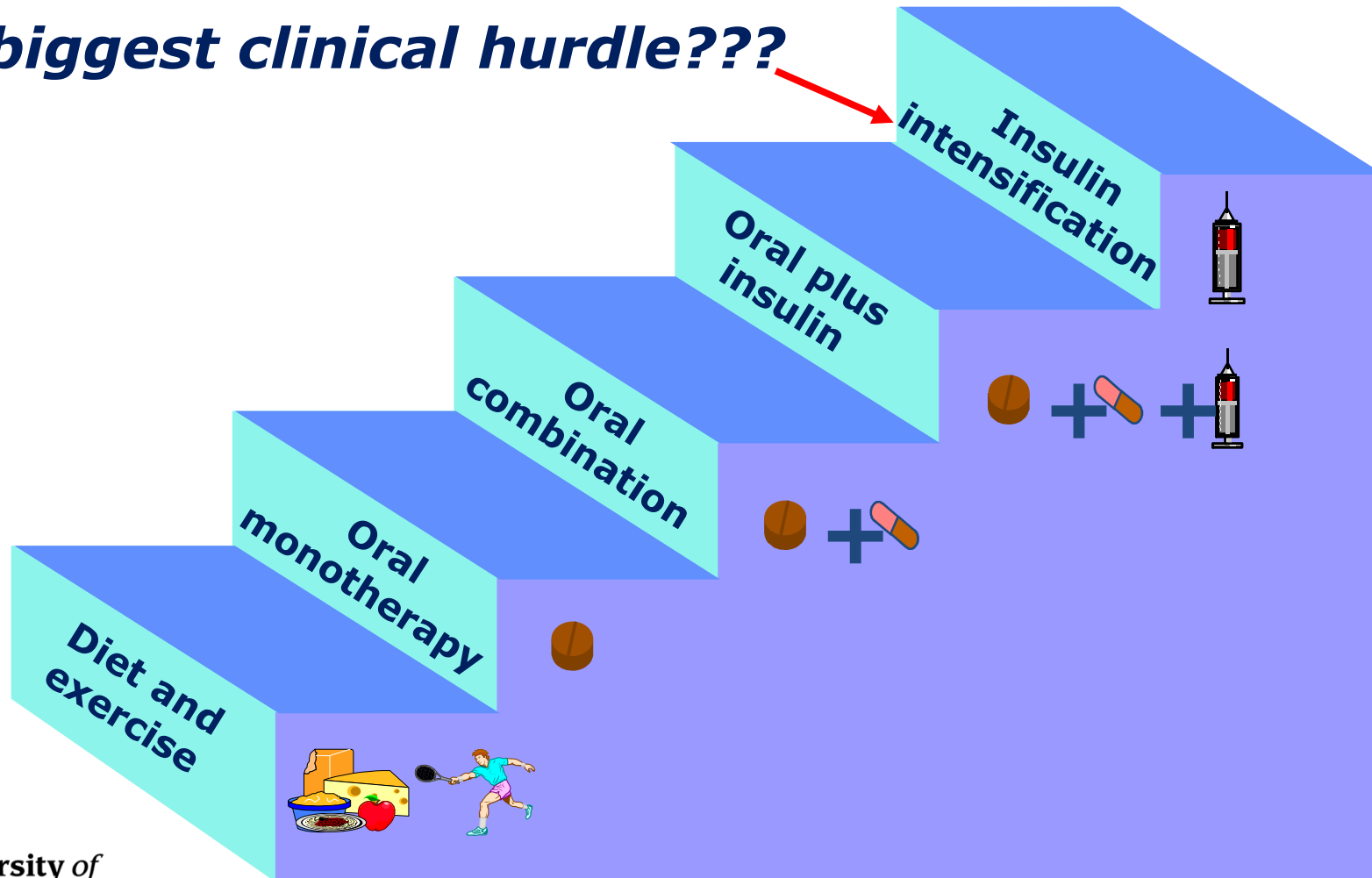
Biggest clinical hurdle???

Clinical hurdle???



Stepwise management of type 2 diabetes

Or biggest clinical hurdle???



What is clinical inertia?

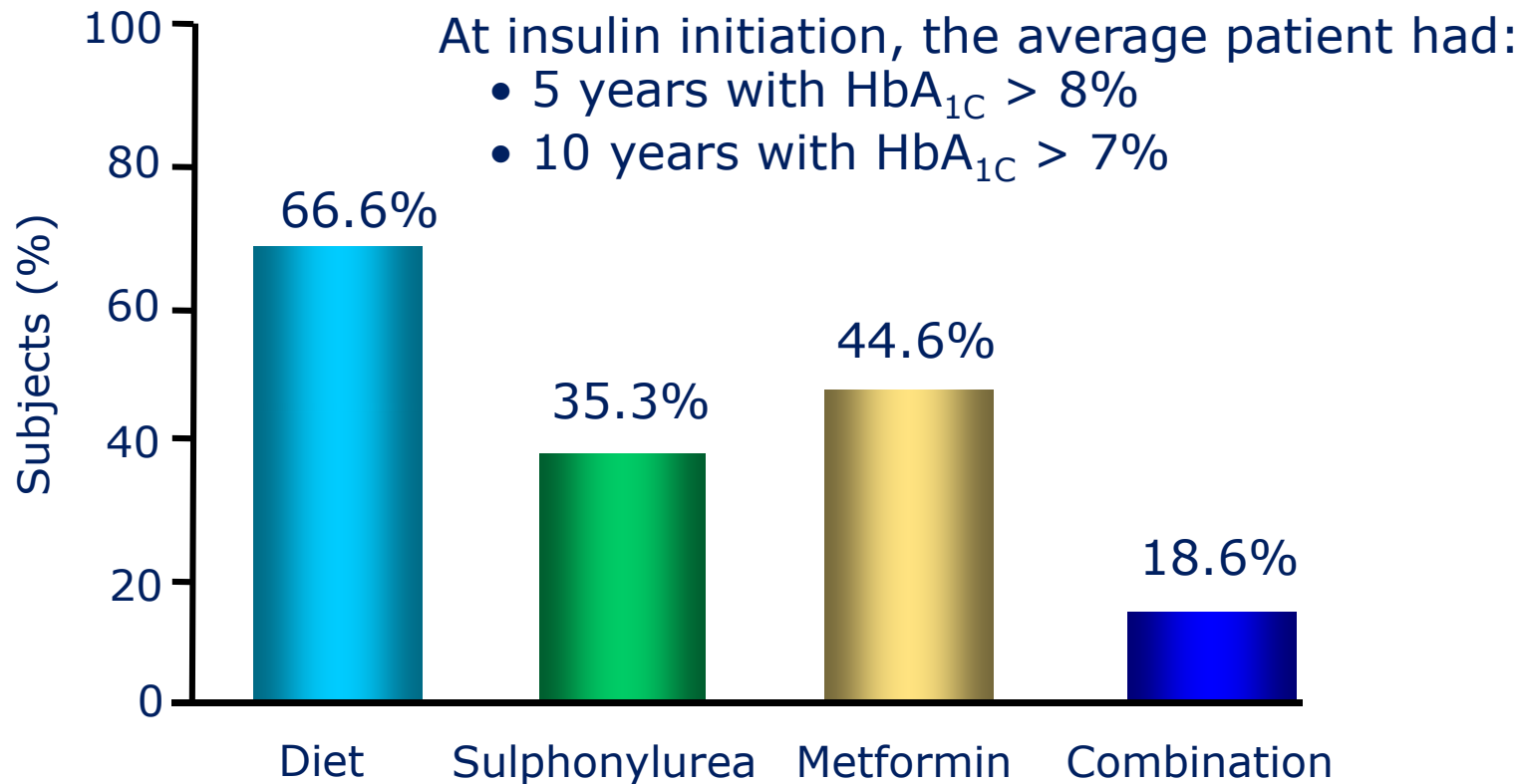
“Failure to advance therapy when required”

- Insulin is often only initiated after years of poor glycaemic control
- Despite TTT trials demonstrating effectiveness and simplicity of adding insulin therapy to treatment regimens
- Multifaceted problem in clinical practice worldwide

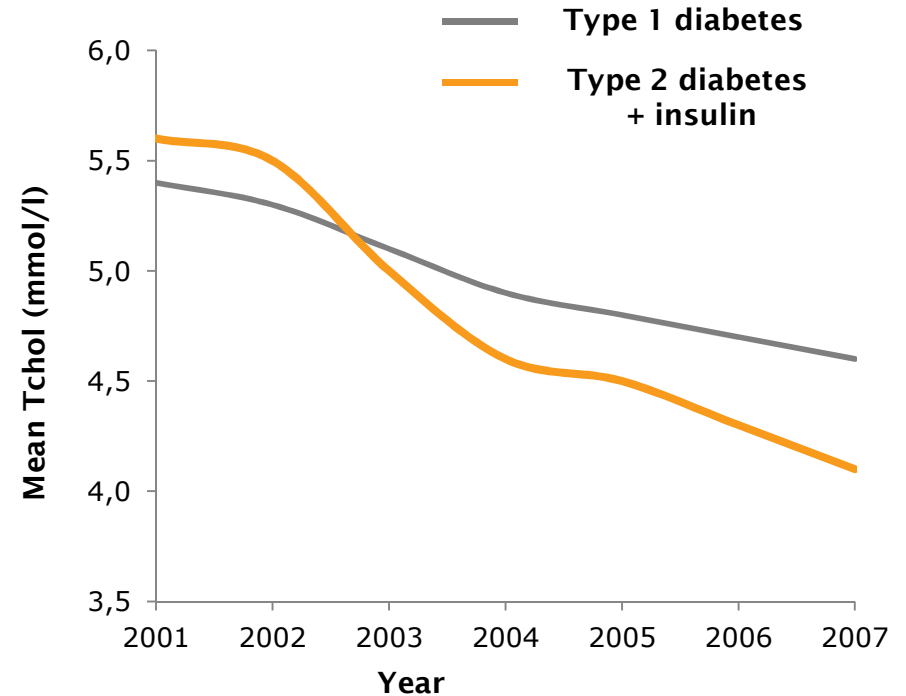
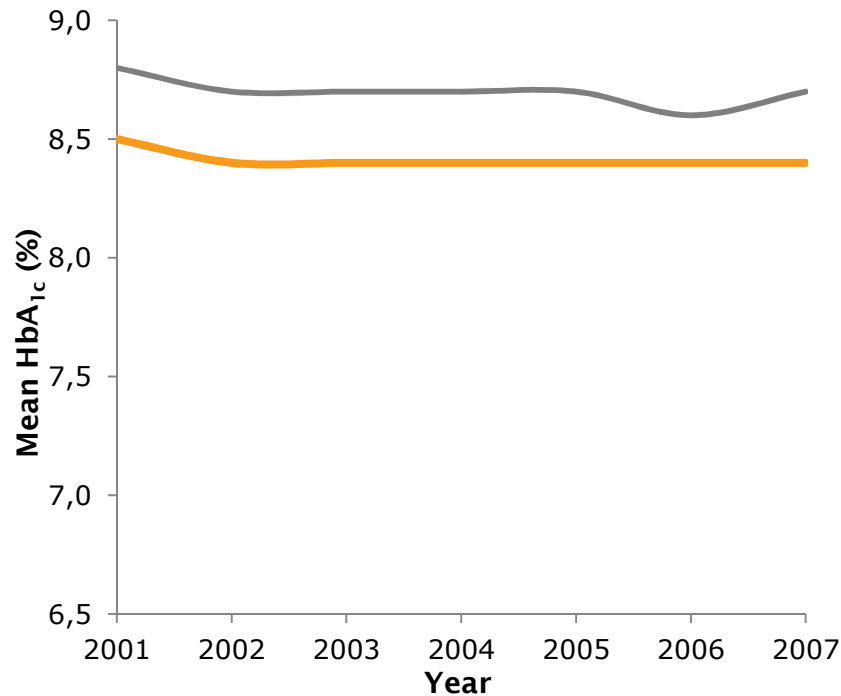


Clinical inertia: “Failure to advance therapy when required”

Percentage of subjects advancing when $HbA_{1C} > 8\%$



Challenges associated with achieving optimal glycaemic goals

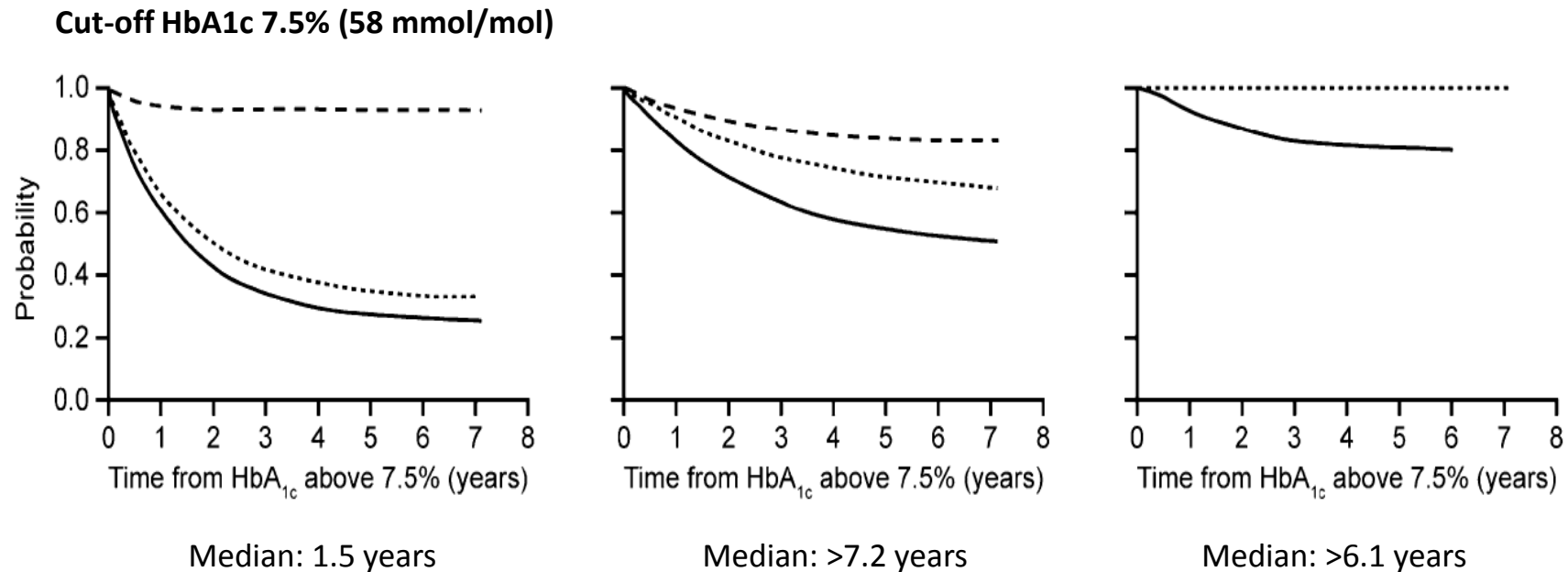


In patients with type 1 diabetes or type 2 diabetes on insulin, there was a 0.1% relative improvement in HbA_{1c} vs. improvements in total cholesterol of 15% and 29%, respectively between 2001 and 2007



Clinical inertia in T2DM

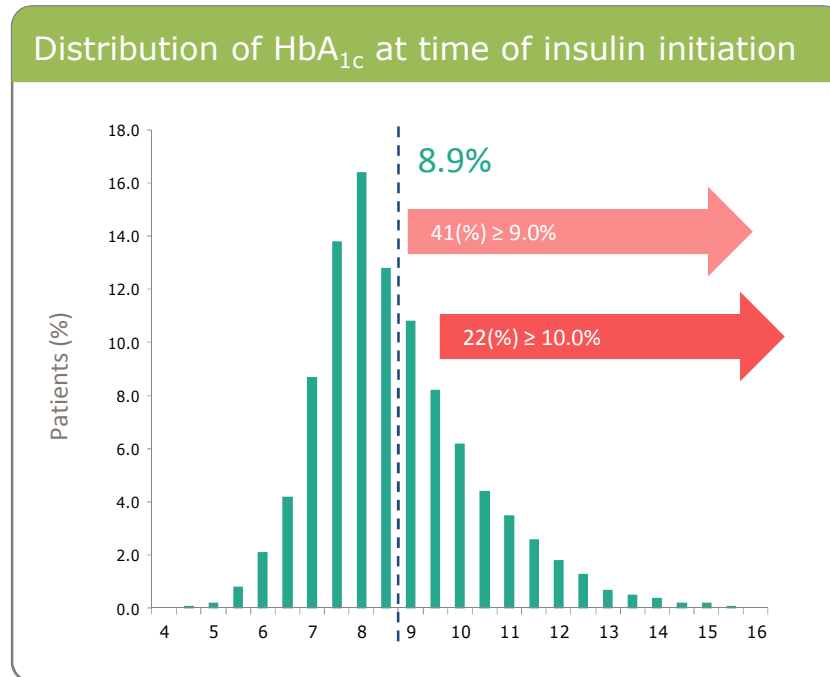
- Retrospective cohort study of over 80,000 people
- Time to treatment intensification from first HbA1c above 7.5%, by number of OADs and type of intensification



*Proportion of people with HbA1c >7.5% having any intensification to their treatment at end of follow-up according to number of OADs



There is a need for earlier insulin initiation – baseline HbA_{1c}



Clinical inertia exists despite:

- The benefits of timely glycaemic control
- Guidelines encouraging earlier use of insulin

At insulin initiation in SOLVE™:

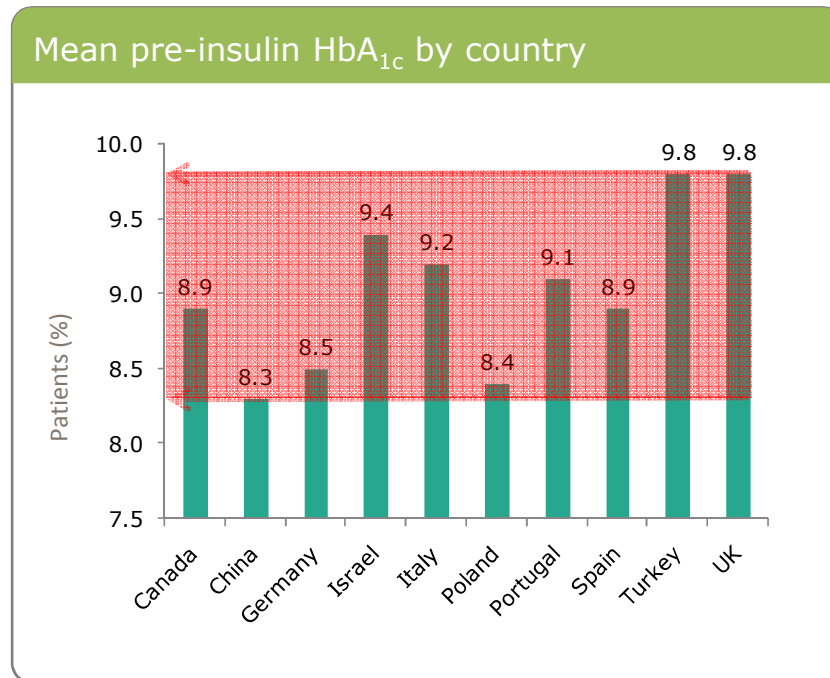
The average HbA_{1c} was 8.9%

41% had HbA_{1c} ≥ 9.0%

22% had HbA_{1c} ≥ 10.0%

Khunti *et al.* *Diab Obes Metabolism* 2012

There is a need for earlier insulin initiation – baseline HbA_{1c} (Countries)



Patients remain poorly controlled on OAD treatment for prolonged periods of time

At insulin initiation in SOLVE™, mean pre-insulin HbA_{1c} range was:

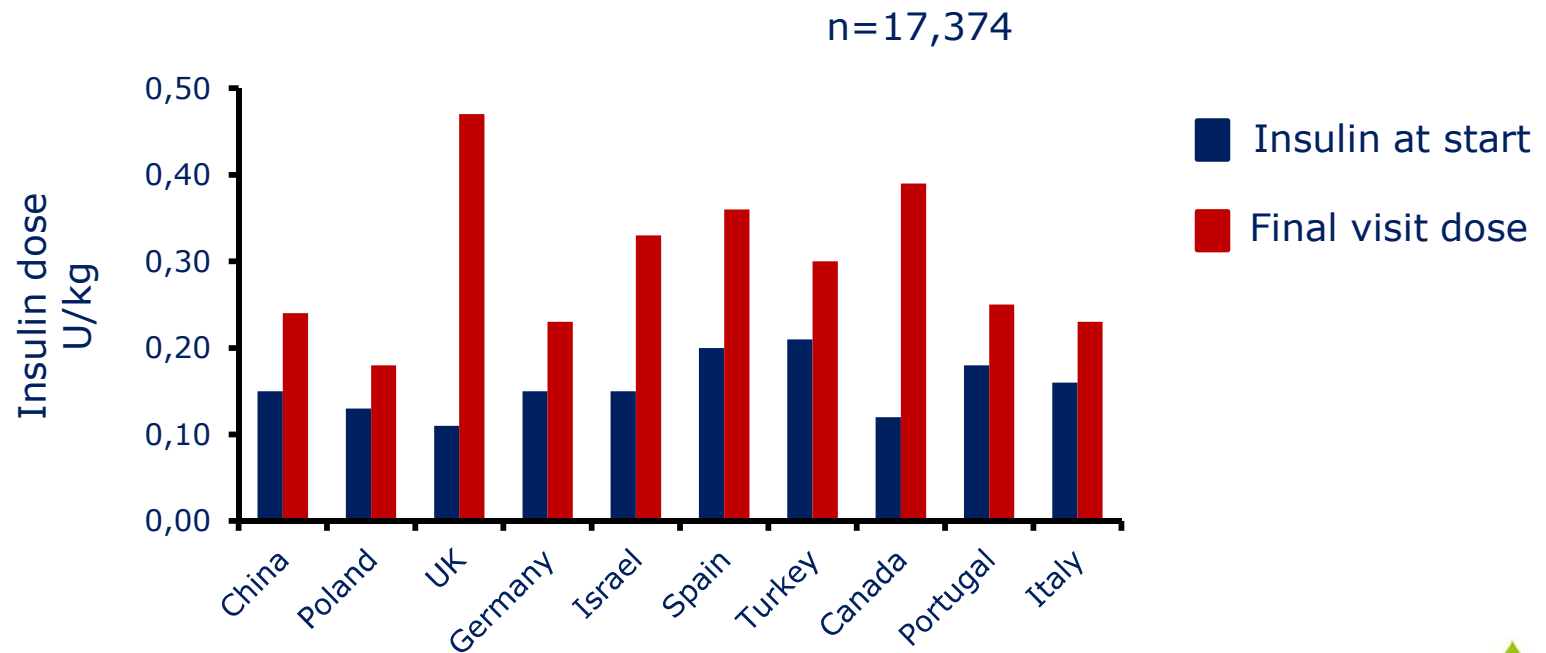
8.3% (China)



9.8% (Turkey/UK)

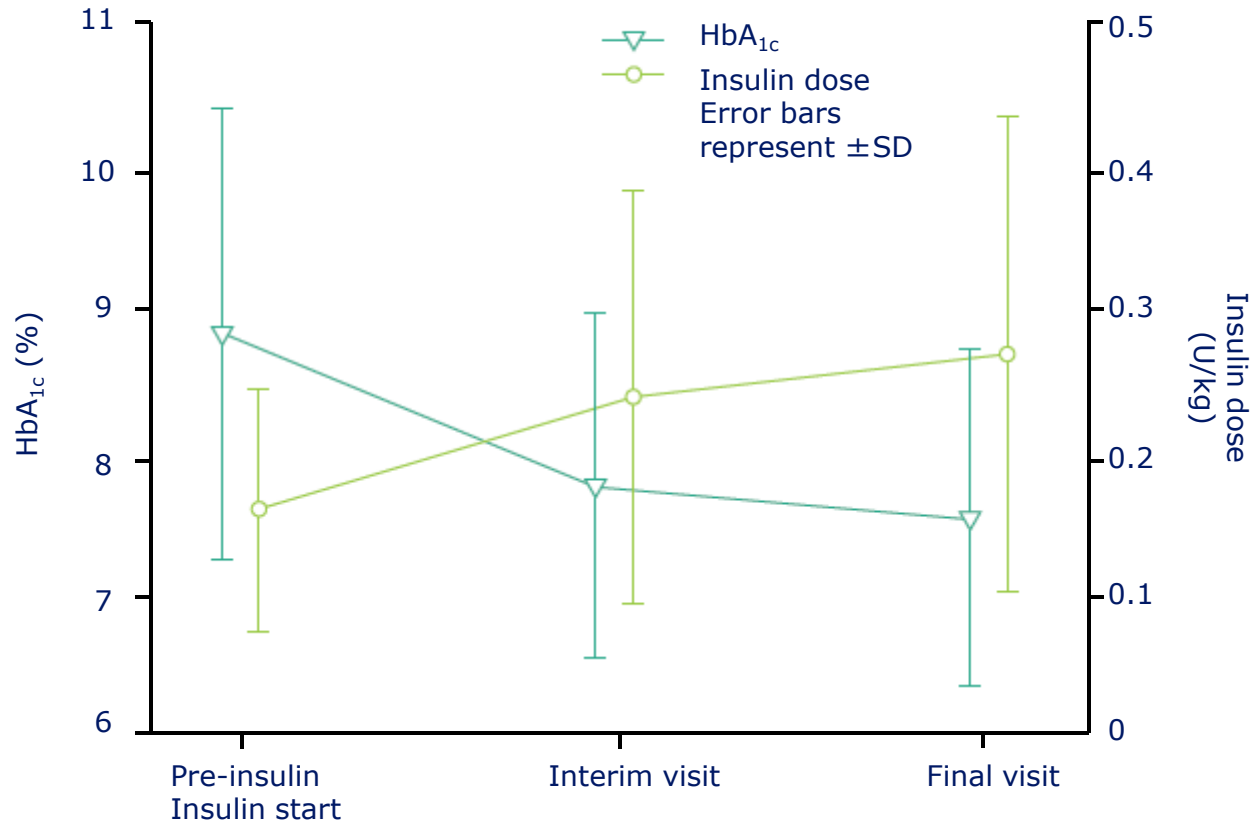
Khunti K et al. Diab Obeity Metabolism 2012

Clinical inertia in T2D in real-life clinical practice (at 24 weeks)



Khunti K et al. Diab Obeity Metabolism 2012

Mean HbA_{1c} and mean insulin dose in the total SOLVE™ cohort



Khunti K et al. Diab Obeity Metabolism 2012



Clinical inertia and CV events

105477 newly diagnosed T2DM (11.3% previous CVD)
5.3 years median follow-up
6 month delay in first 2 years of treatment with HbA1c > 7.0%

	MI	Stroke	HF	Any CVE
All patients	1.38 (1.16-1.82)	1.07 (0.89-1.29)	1.28 (1.10-1.48)	1.25 (1.13-1.39)
No Previous CVD	1.21 (1.00-1.47)	1.07 (0.87-1.31)	1.28 (1.07-1.52)	1.20 (1.07-1.35)
Previous CVD	1.91 (1.40-2.60)	1.08 (0.73-1.61)	1.27 (0.95-1.70)	1.42 (1.15-1.75)

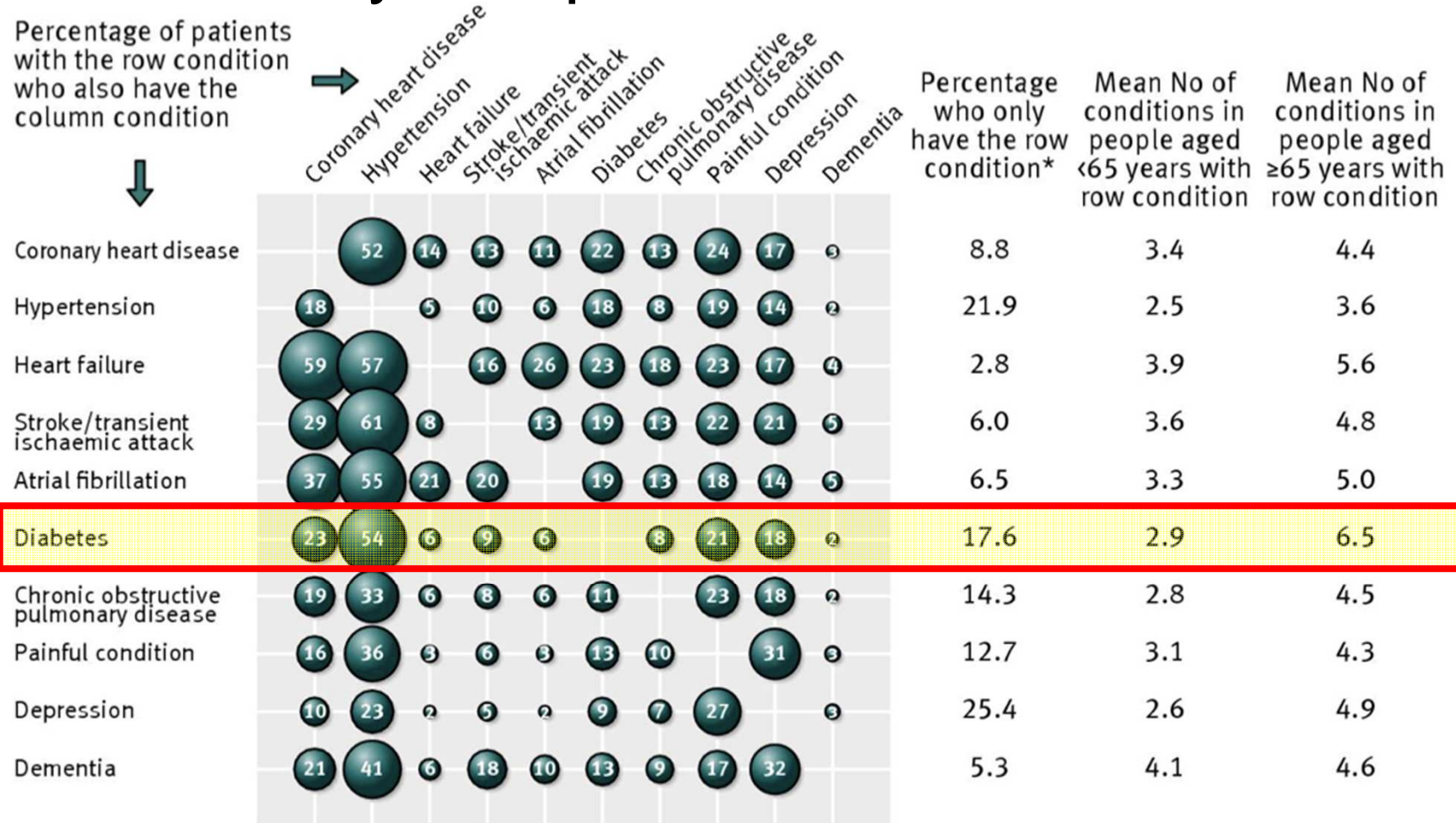
Values in table correspond to HR (95% CI)

Issues that underpin clinical inertia

- Multimorbidity
- Hypoglycaemia
- Complex regimens
- Data about perceived insulin outcomes
- Lack of patient adherence to treatment
- Lack of education
- Financial incentives



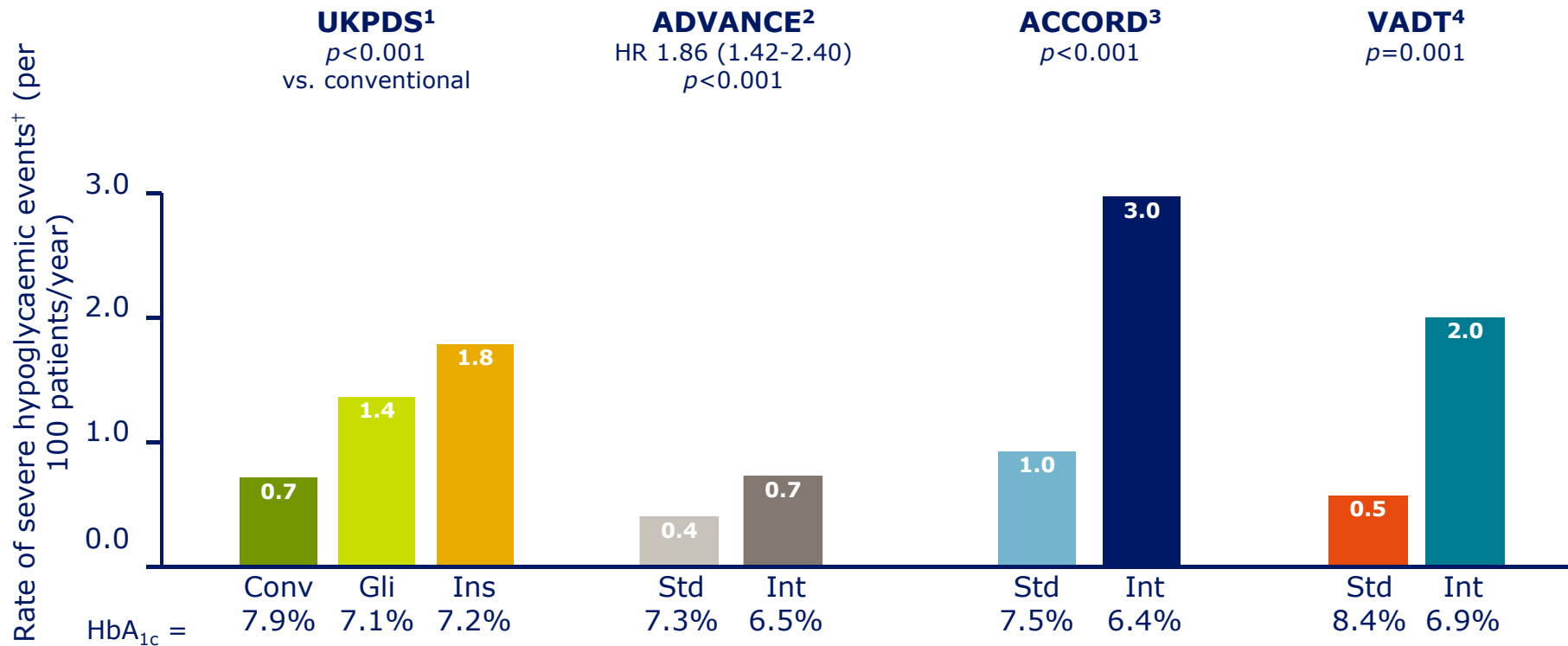
Comorbidity of top 10 common conditions



* Percentage who do not have one of 39 other conditions in the full count



Higher rate of severe hypoglycaemia with intensive glycaemic control*



*Intensive glycaemic control was defined differently in these trials
 †Hypoglycaemia requiring any assistance in glucose-lowering trials
 Conv, conventional therapy; gli, glibenclamide; HR, hazard ratio; ins, insulin; int, intensive therapy; std, standard therapy



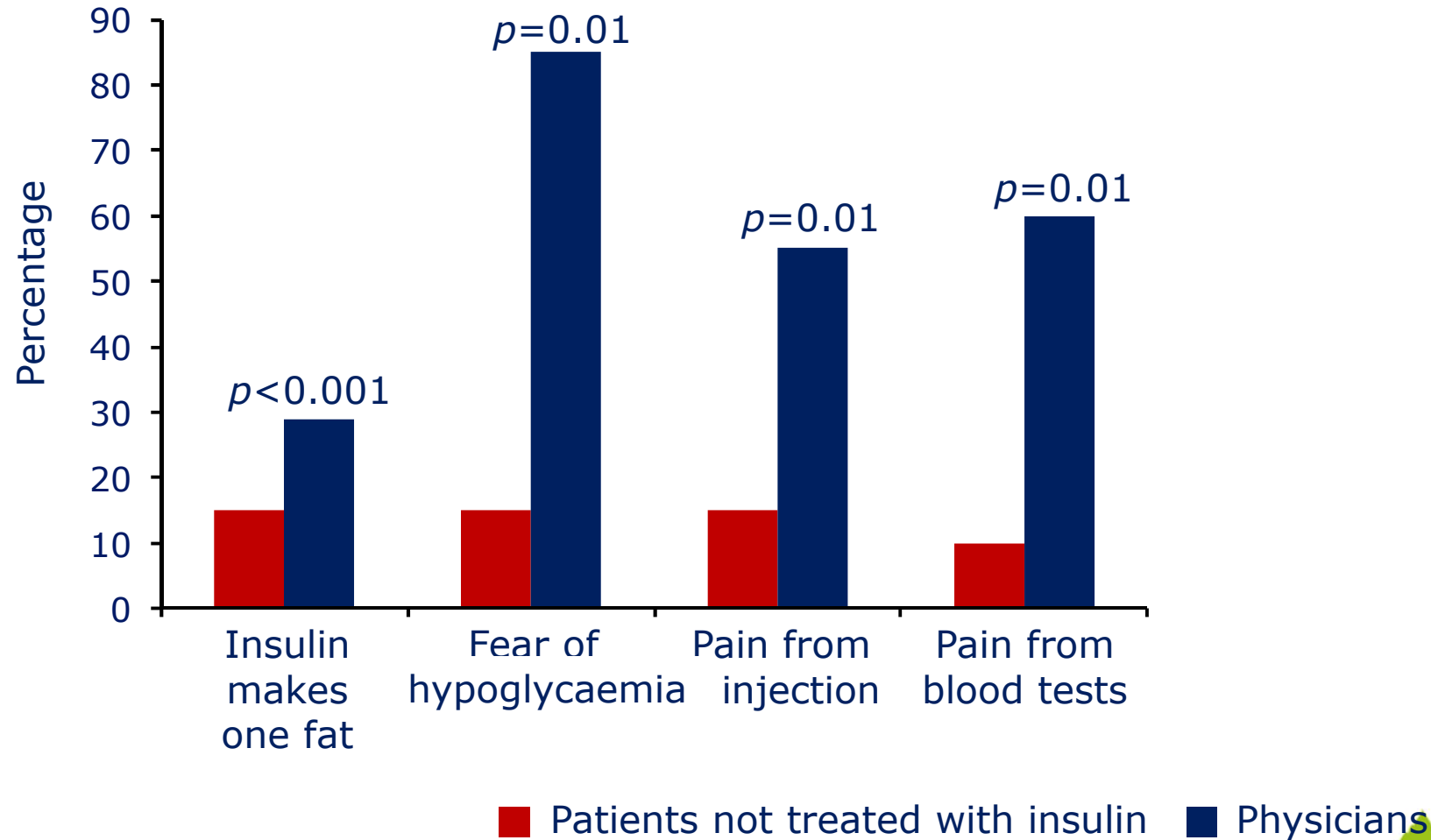
Physician barriers

- Physicians may be reluctant to initiate insulin due to:¹⁻³
 - beliefs about patient risk
 - excess weight gain
 - risks in patients with comorbidities
 - hypoglycaemia
 - impaired quality of life
 - resource issues
 - beliefs about patient competence

1. Peyrot *et al.* *Diabetes Care* 2005;28:2673–9; 2. Elgrably *et al.* *Diabet Med* 1991;8:773–7; 3. Wallace & Matthews. *QJM* 2000;93:369–74

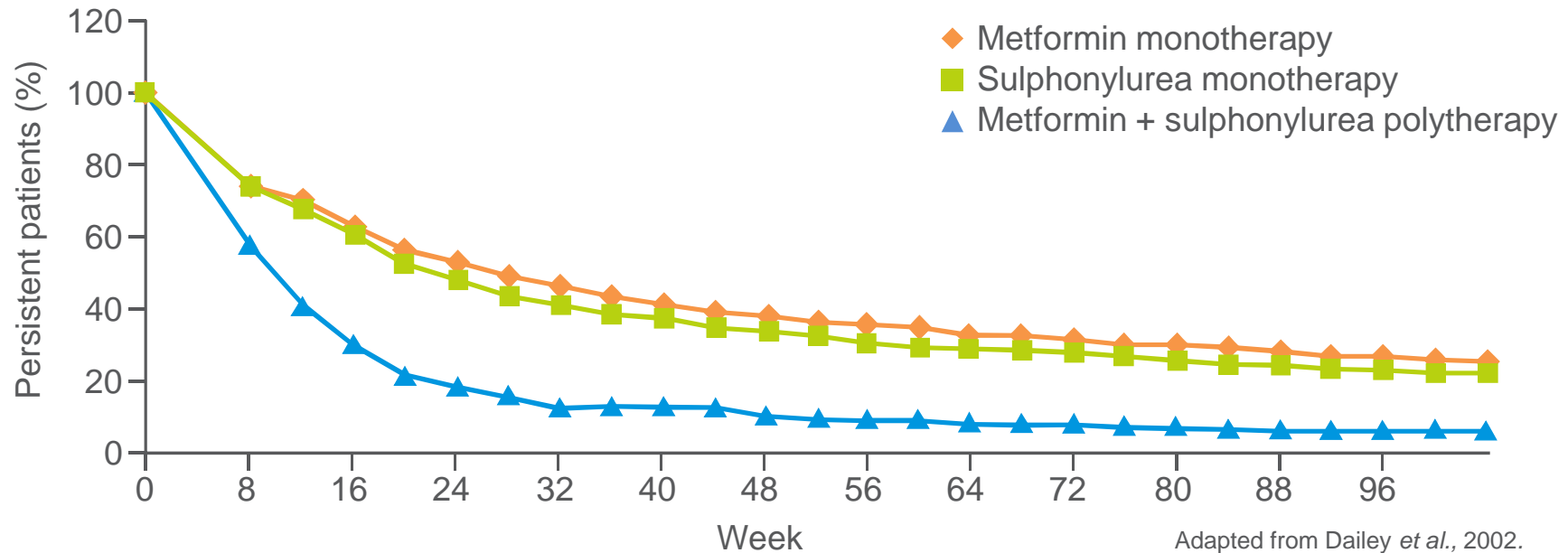


Barriers to insulin initiation



Many patients with diabetes do not adhere to their treatment

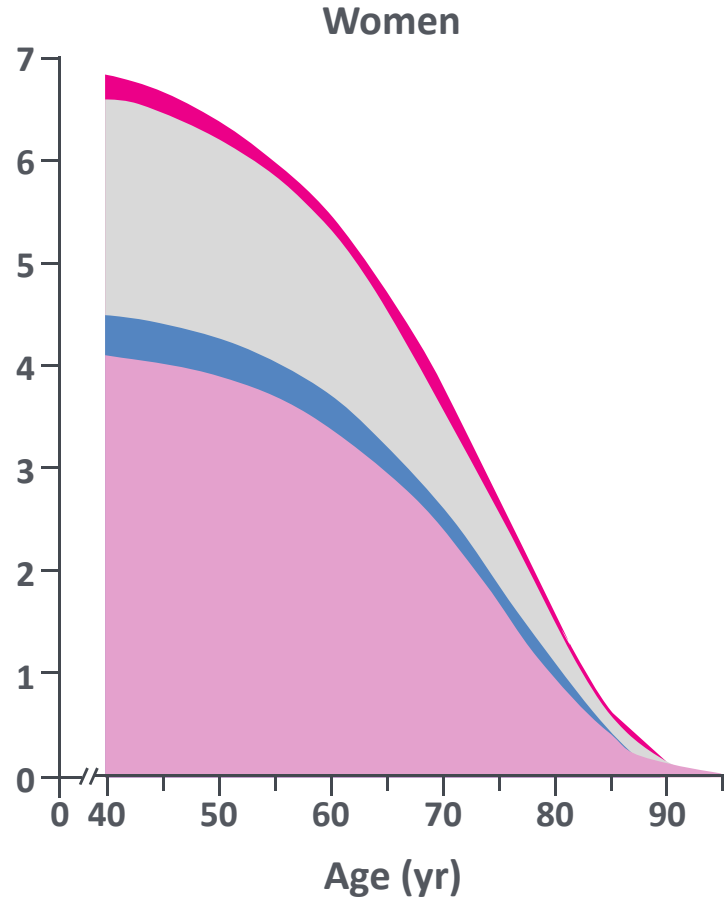
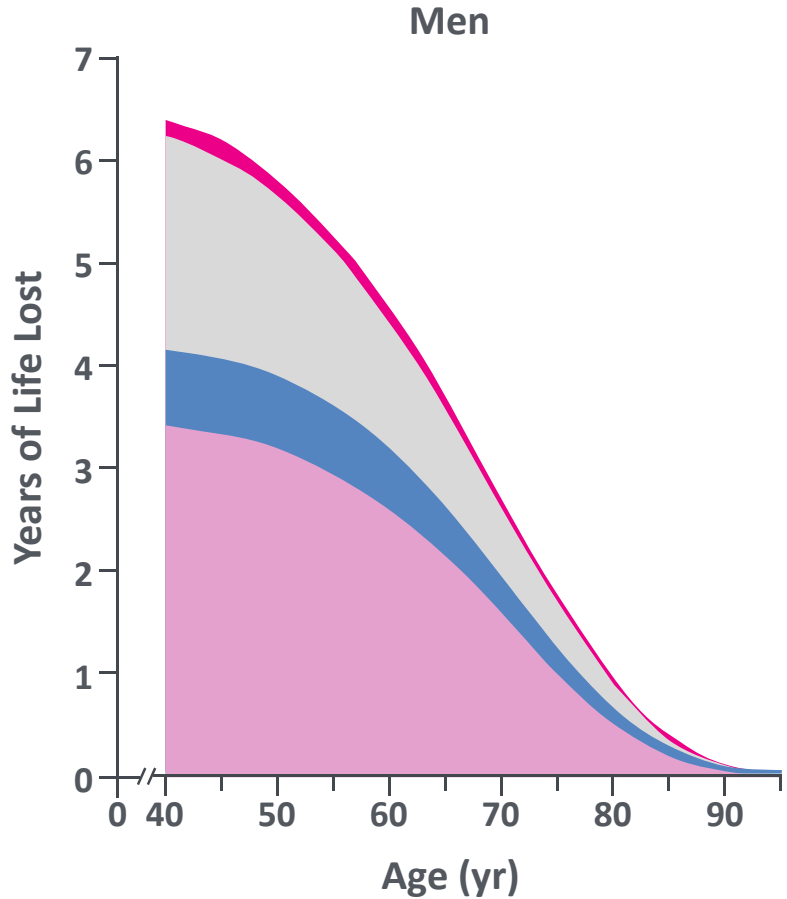
- Poor patient adherence is an important barrier to glycaemic control¹
- Retrospective studies in people with Type 2 diabetes reported adherence rates of 36–93% for oral agents and 62–64% for insulin¹
- Therapy persistence has been shown to decrease with time, and with polytherapy compared with monotherapy²



© Leicester Diabetes Centre 2012



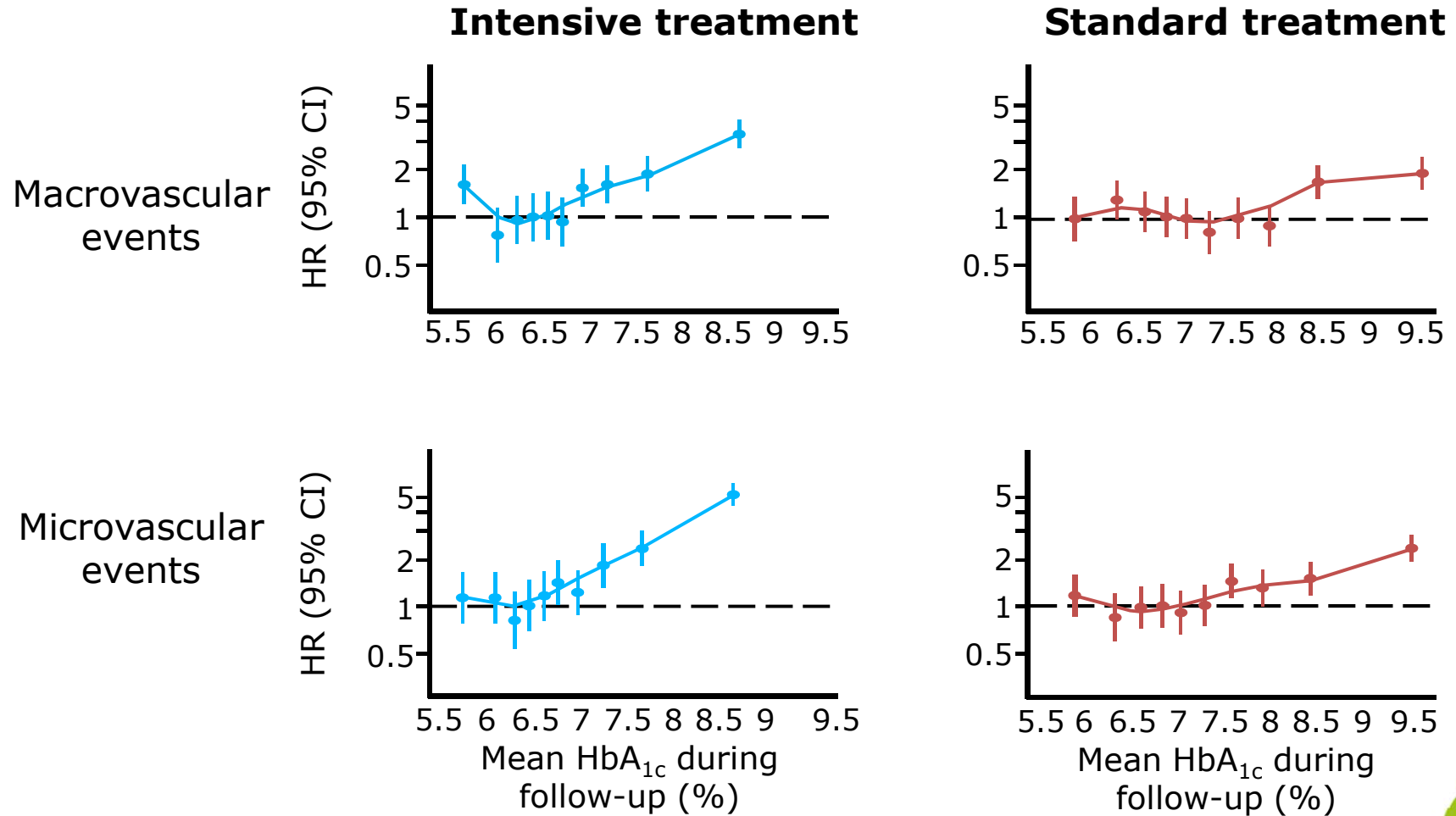
Elderly patients




■ Death from unknown causes
 ■ Noncancer, nonvascular deaths
 ■ Cancer deaths
 ■ Vascular deaths



ADVANCE: HbA_{1c} vs. major macrovascular and microvascular event outcome

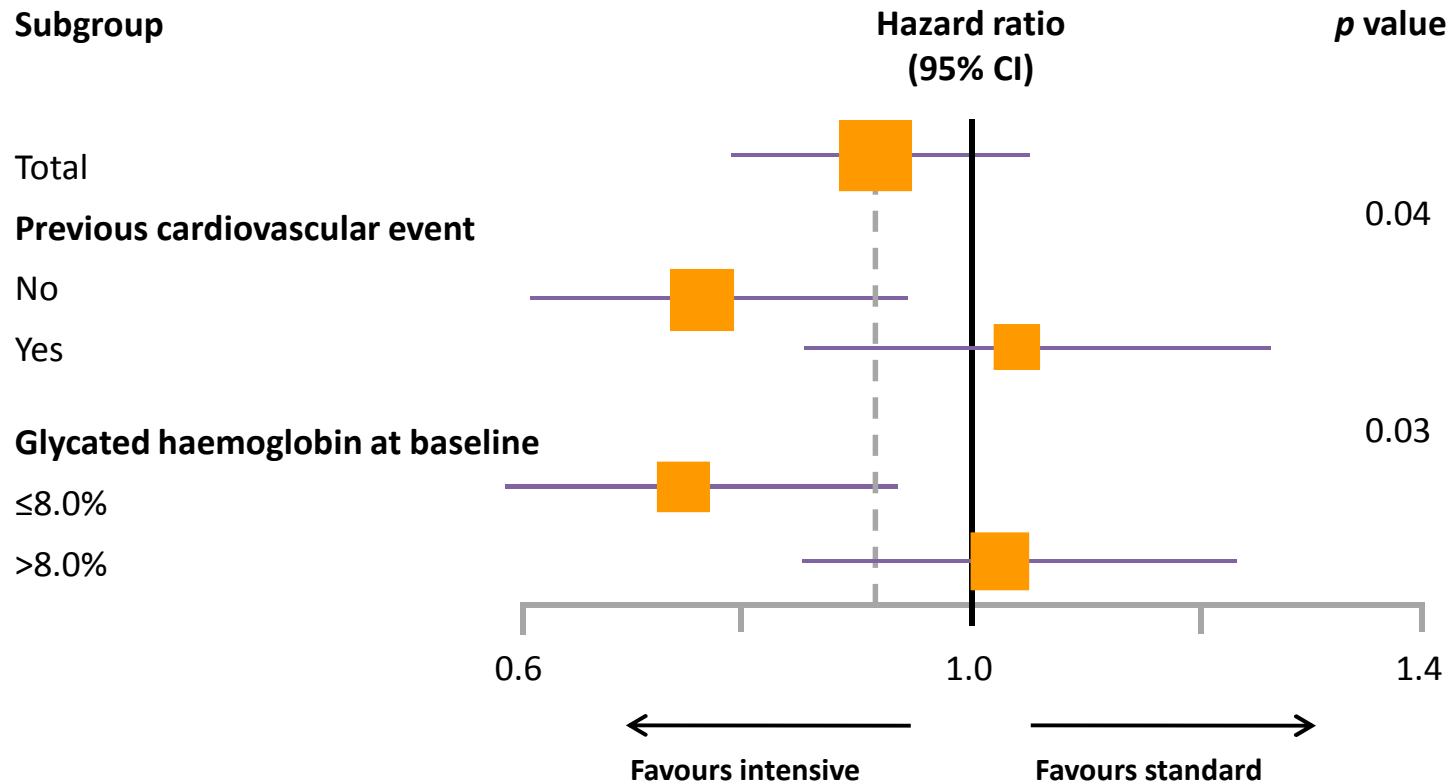



 Mean age 66 years
 CI confidence interval; HR, hazard ratio
 Zoungas S, et al. *Diabetologia* 2012;55:636-43.



ACCORD: Intensive glucose control beneficial in patients with no previous CVD or HbA1c <8%

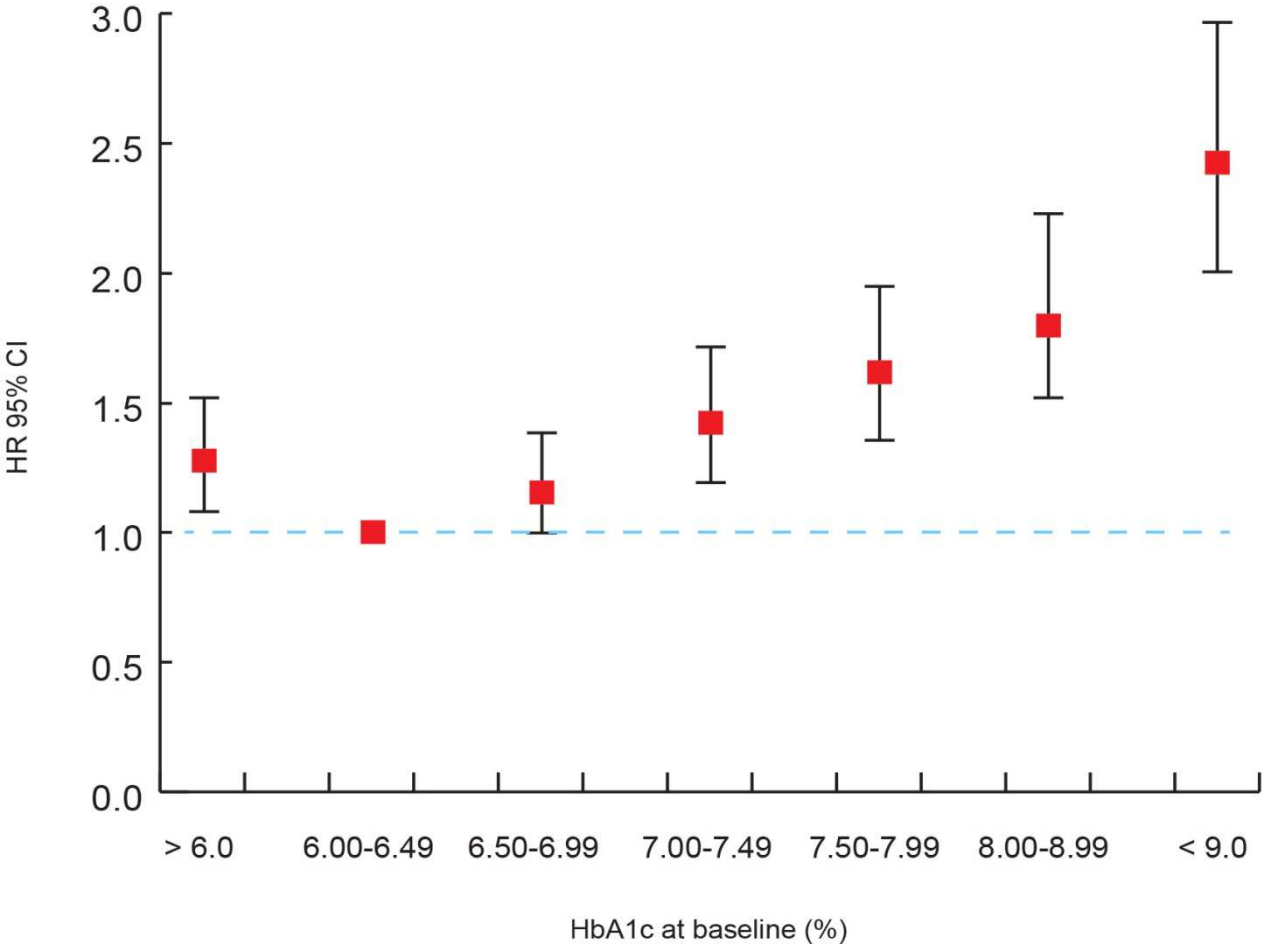
Primary outcome



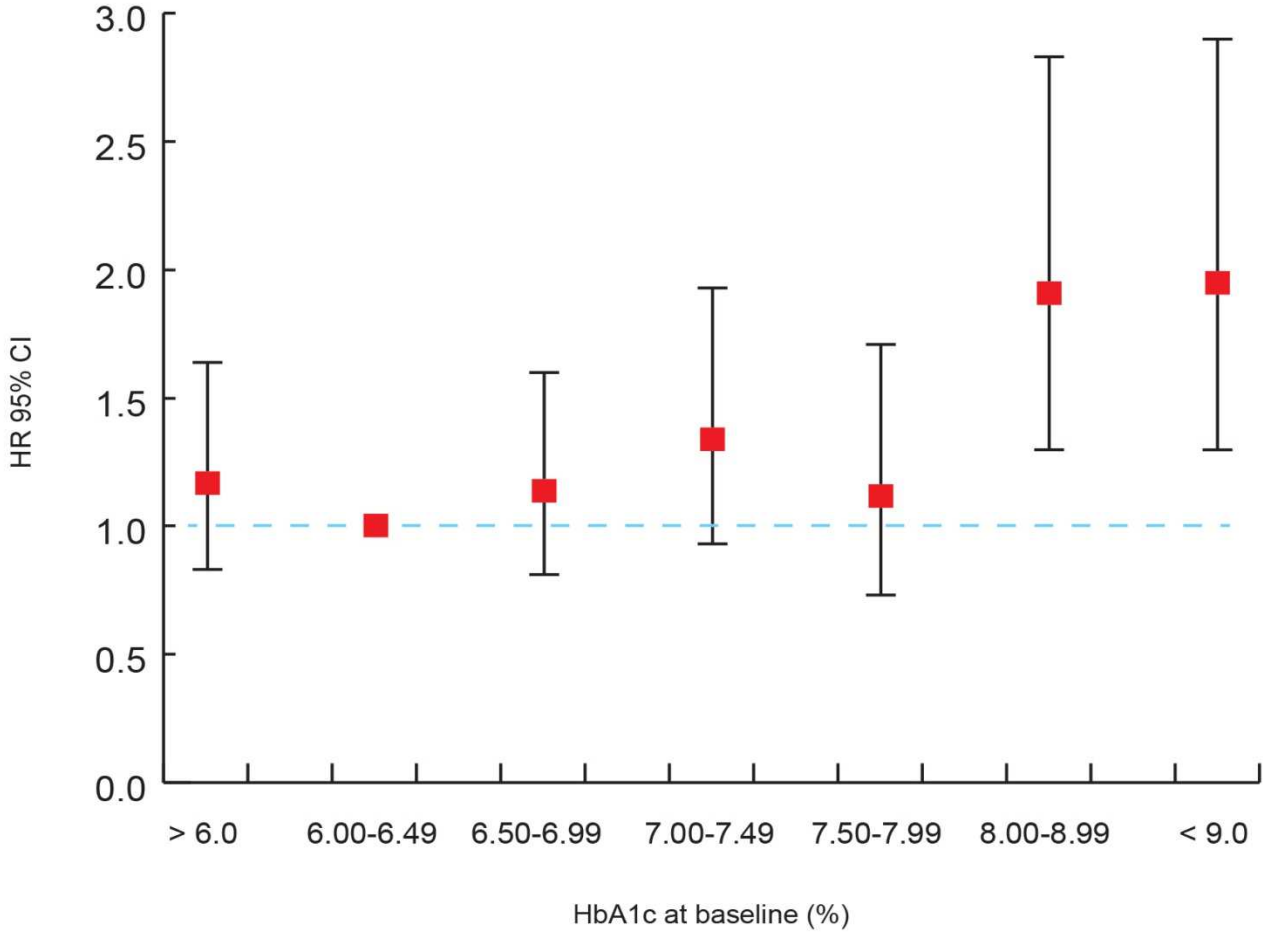
The vertical dashed line indicates the overall hazard ratio.
The size of each square is proportional to the number of patients.



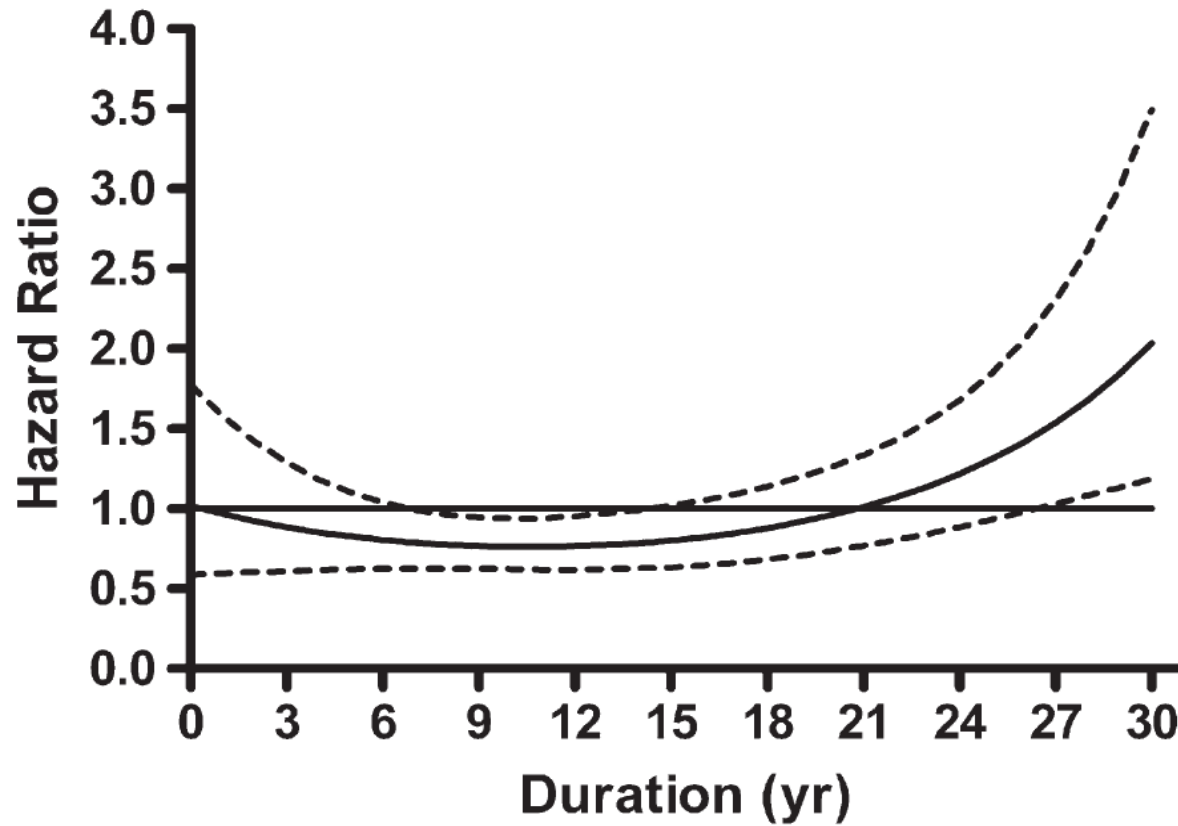
Individuals without cardiovascular disease



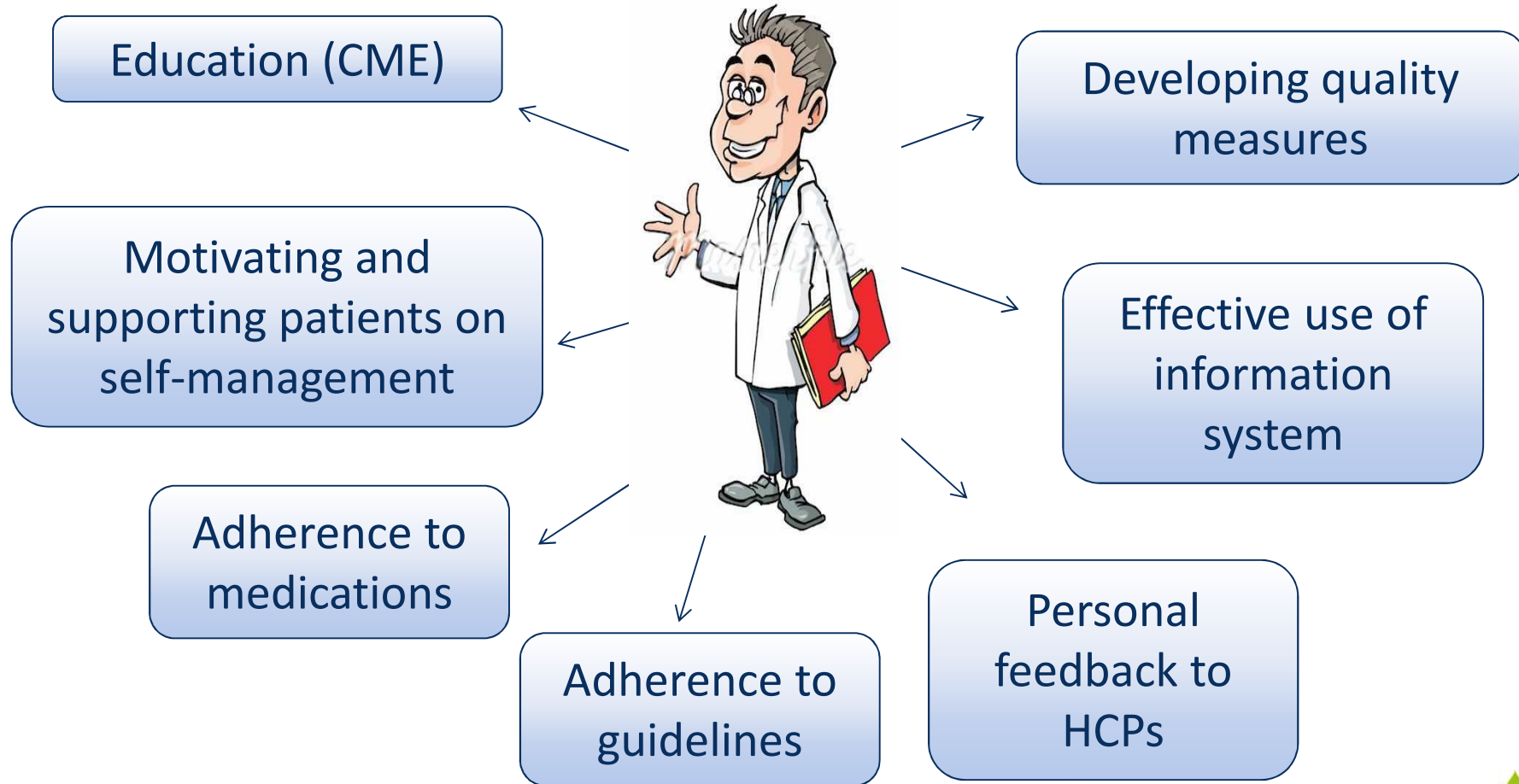
Individuals with cardiovascular disease



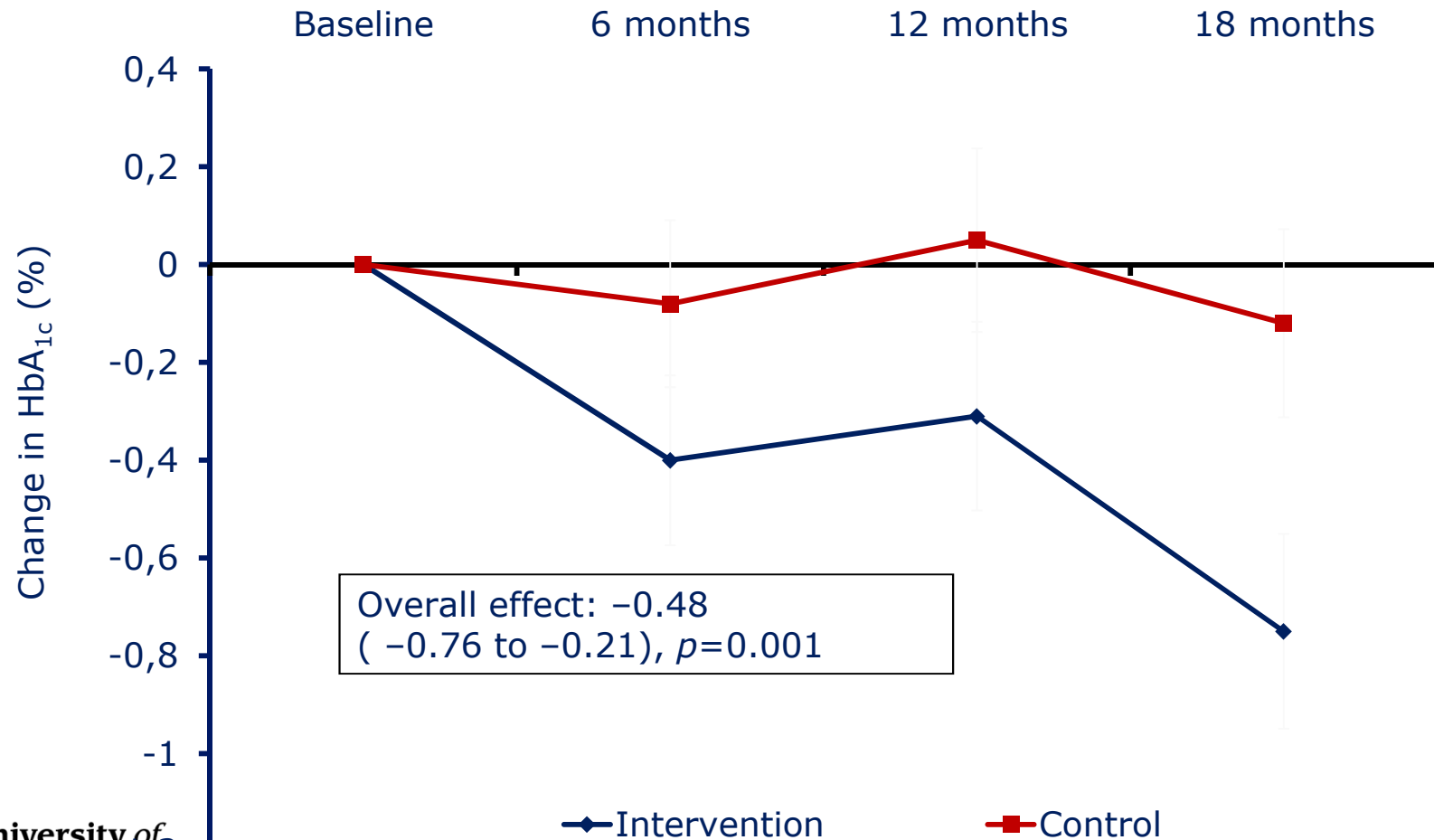
Duration of diabetes and CVD risk in VADT



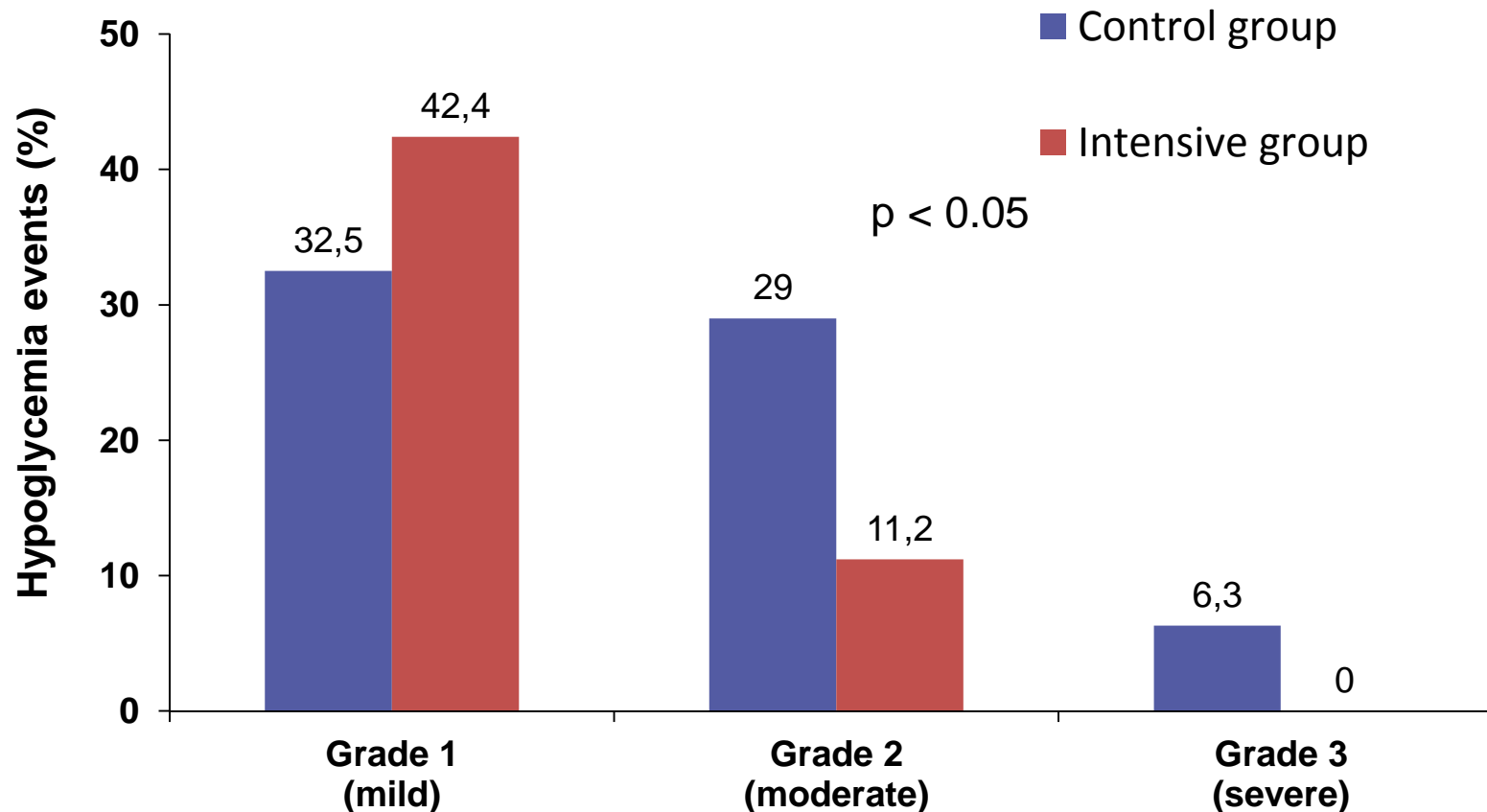
How can we improve the achievement of HbA_{1c} targets?



Multifactorial intervention in individuals with type 2 diabetes and microalbuminuria: MEMO study



Impact of education on hypoglycaemia



Grade 1 (minor) hypoglycaemia was defined as the presence of hypoglycaemic symptoms with a self-measured capillary blood glucose of 3.1 mmol/L and self-treated; **Grade 2 (moderate)** hypoglycaemia was defined as a self-measured plasma glucose of < 3.1 mmol/L and self-treated; **Grade 3 (major)** hypoglycaemia was defined as requiring the assistance of another person.

Tratamiento intensivo precoz

- Guías/recomendaciones Tto. Diabetes
- “La vida real”
- Complejidad de la individualización
- Tratamiento intensivo precoz
- **Take-home** messages

Mixed results on tight and rapid HbA1c control

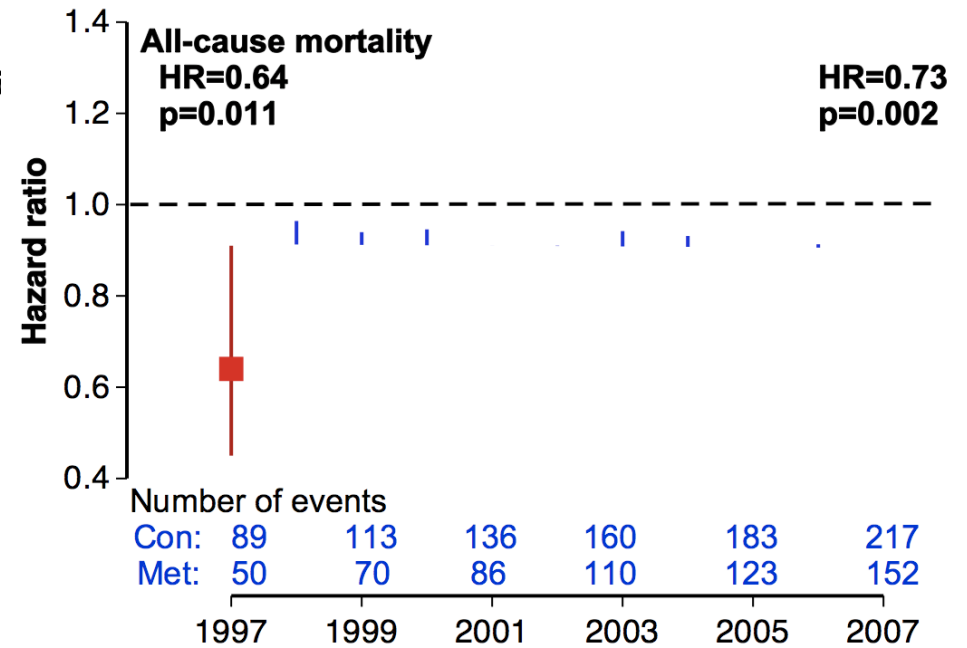
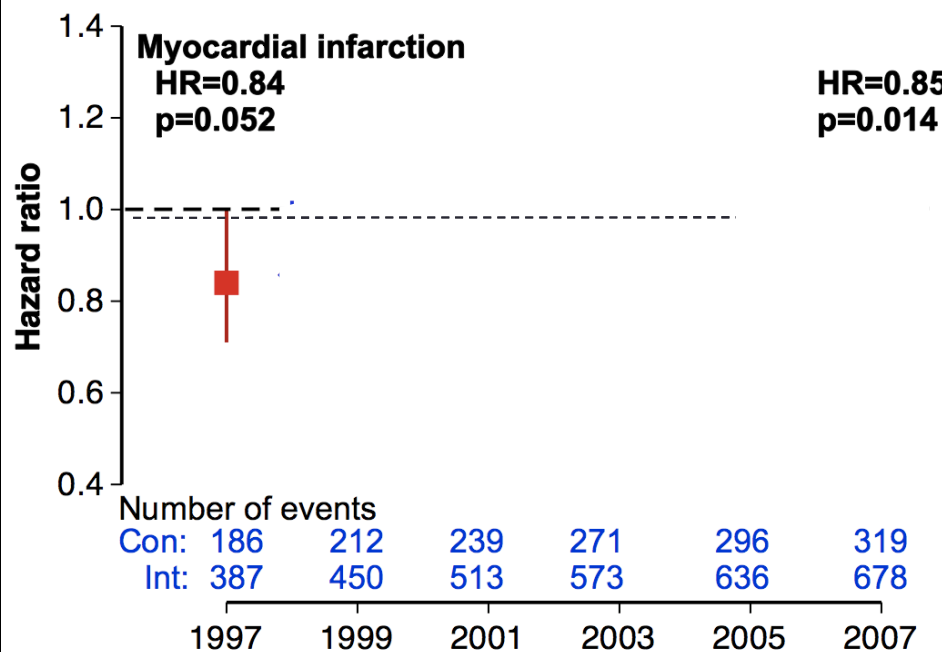
Study	HbA1c (%)		Impact of intensive therapy vs standard therapy on outcome		
	Standard therapy	Intensive therapy	Microvascular	CVD	Mortality
ACCORD	7.5	6.4	?	↔	↑
ADVANCE	7.3	6.5	↓	↔	↔
VADT	8.4	6.9	↔	↔	↔
UKPDS	7.9	7.0	↓	↔	↔
UKPDS – follow-up	~7.9	~7.9	↓	↓*	↓

ACCORD Study Group. *N Engl J Med* 2008;358:2545-2559;
 ADVANCE Collaborative Group. *N Engl J Med* 2008;358:2560-2572;
 Duckworth W, et al. *N Engl J Med* 2009;360:129-139;
 UKPDS. *Lancet* 1998;352:837-853;
 Holman RR, et al. *N Engl J Med* 2008;359:1577-1589.

“The legacy effect”

SU / Insulina

Metformina

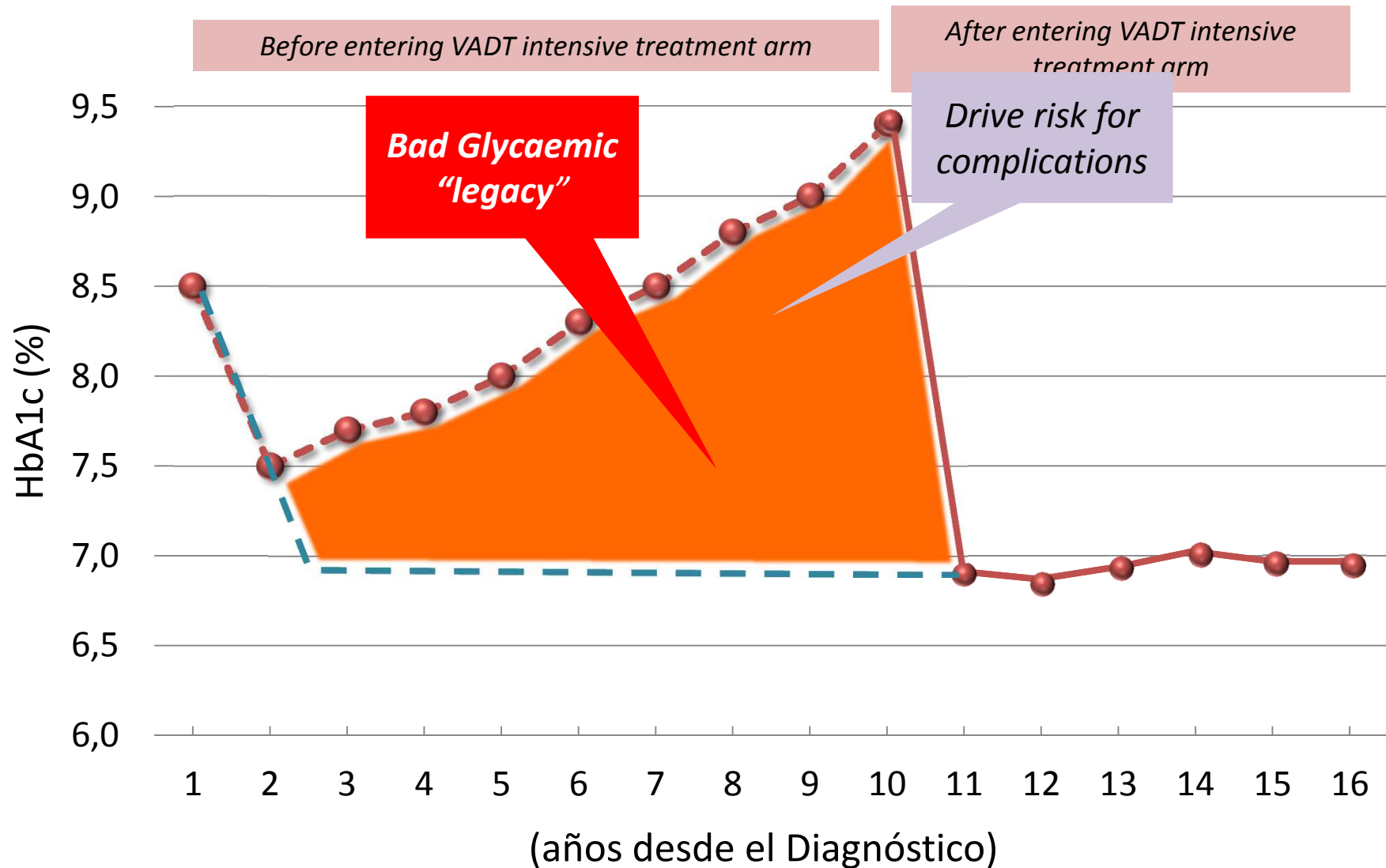


Holman RR et al. *N Engl J Med.* 2008;359:1577–1589

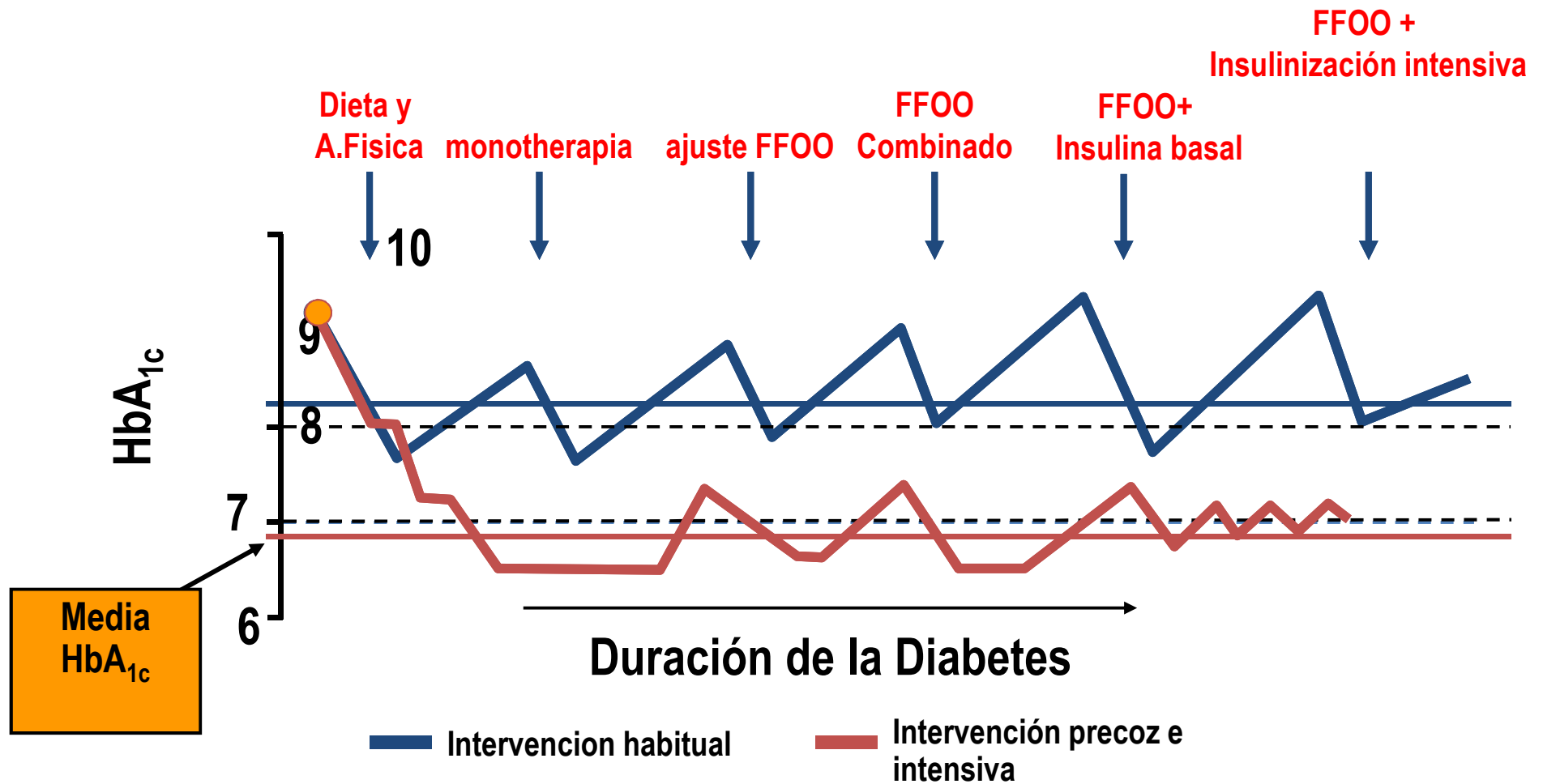
*De Vries JH *Diabetologia.* 2011;54:705–706

Consecuencias de la demora de la intervención

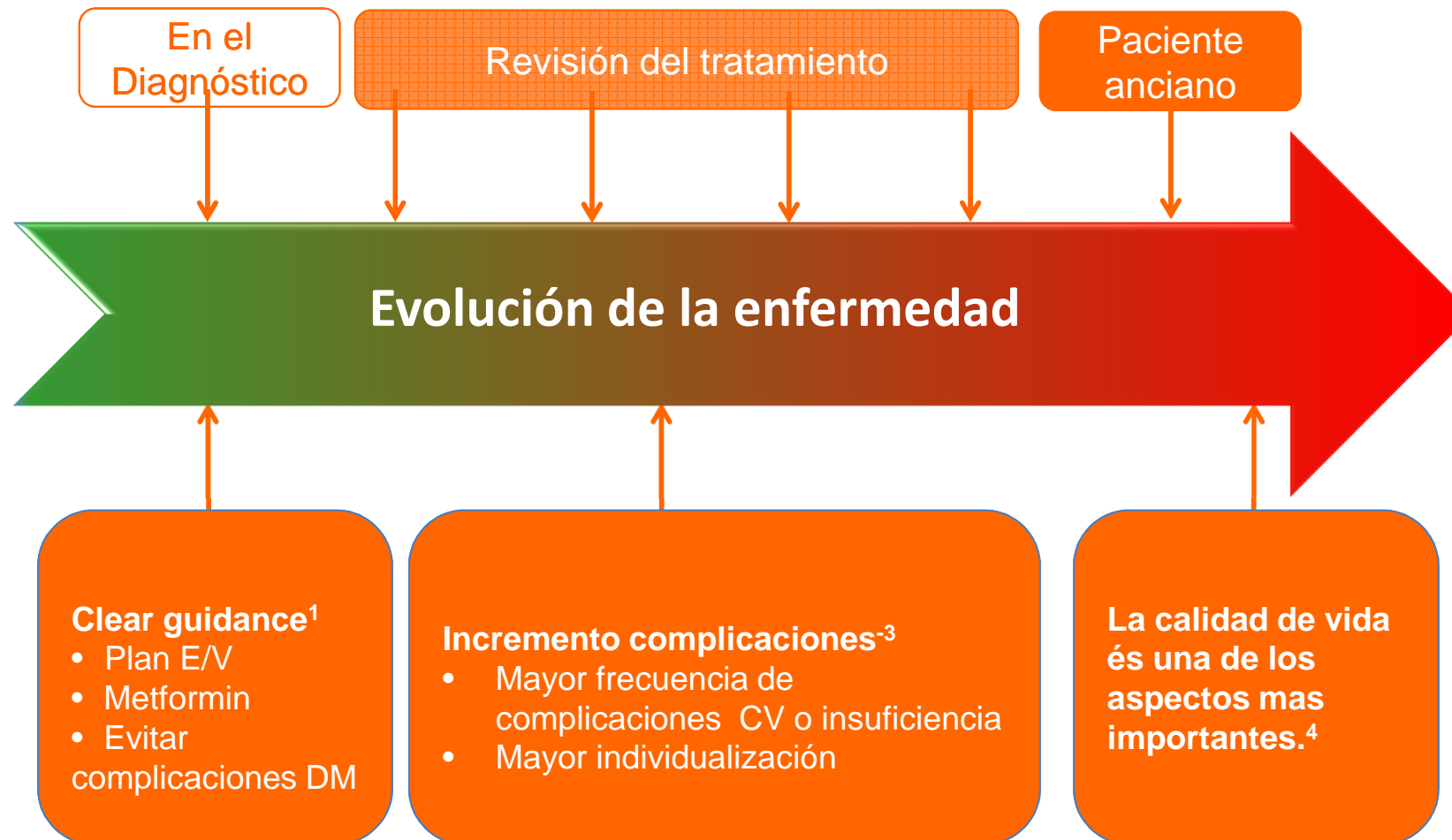
Interpretación de VADT



Intervención precoz / logro de objetivos?

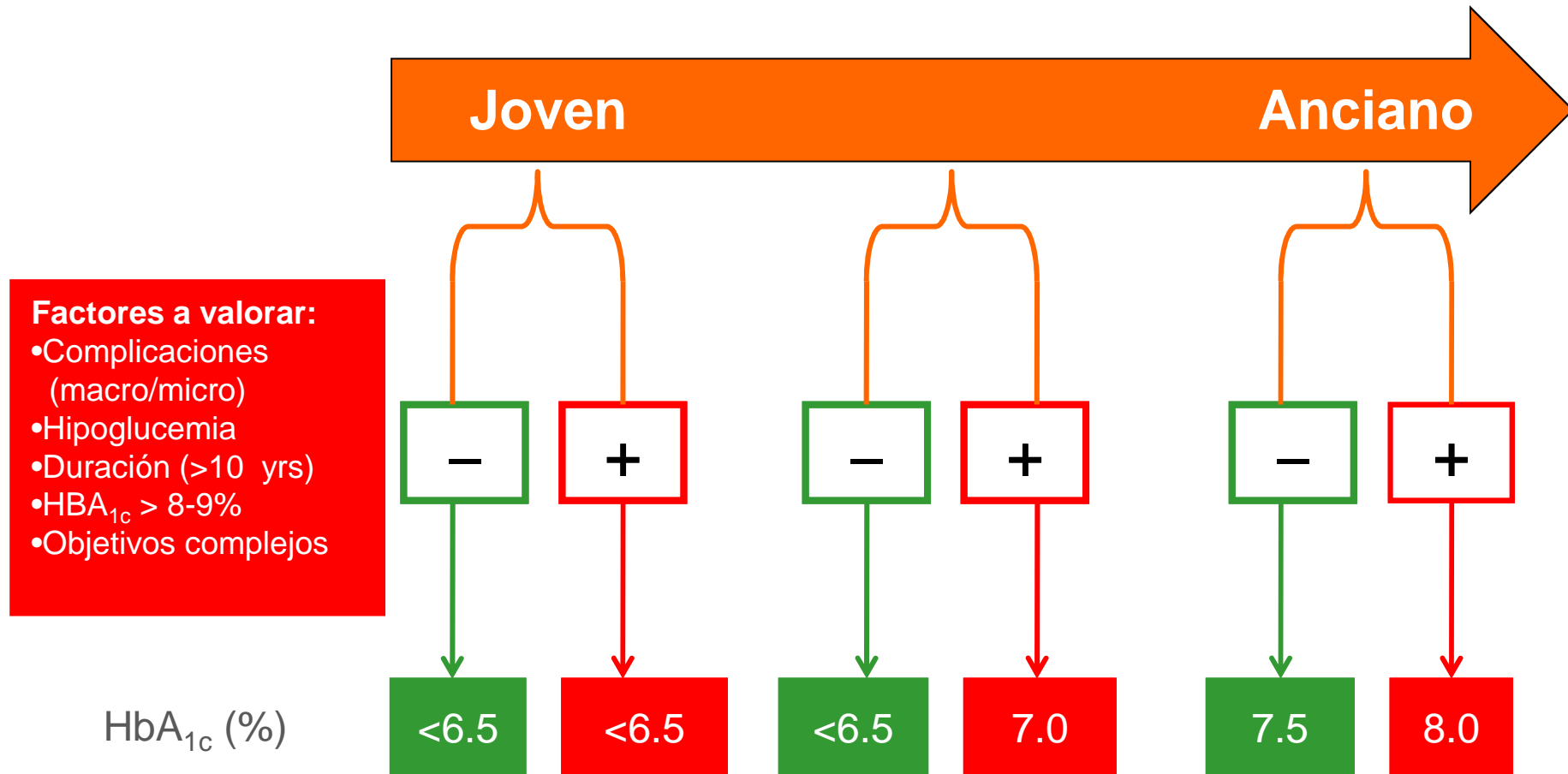


Complejidad progresiva del manejo de la DM2



1,2. Adapted from National Institute for Health and Clinical Excellence. Clinical Guideline 87. Type 2 diabetes – newer agents (a partial update of CG66): quick reference guide. NICE clinical guideline 66: Type 2 Diabetes Management. Available at: <http://www.nice.org.uk/nicemedia/pdf/CG66NICEGuideline.pdf> (accessed November 2012).
3. Go AS, et al. *N Engl J Med.* 2004;351:1296–1305; 4. Morley JE. *Diabet Med.* 1998;15 (Suppl. 4): S41–6.

Individualización terapéutica



Take-home messages

- Las guías y recomendaciones actuales recomiendan un **control glucémico estricto** desde las **fases iniciales** de la enfermedad
- Existen varias **barreras** que **dificultan** un control estricto
- Son **necesarias** diferentes **soluciones** desde diversos areas
- Las **estrategias** incluyen
 - **Mejorar los conocimientos** y su **implementación** por sanitarios y pacientes
 - Proporcionar **ayudas** de **prescripción**
 - **Incrementar** la eficiencia del **trabajo en equipo**
 - **Comunicación**



Gracias

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