Individualized therapy in diabetes

Antonio Ceriello

Insititut d'Investigacions Biomèdiques
August Pi i Sunyer (IDIBAPS)
Barcelona
Spain

IDIBAPS
Institut
D'Investigacions
Biomèdiques
August Pi i Sunyer

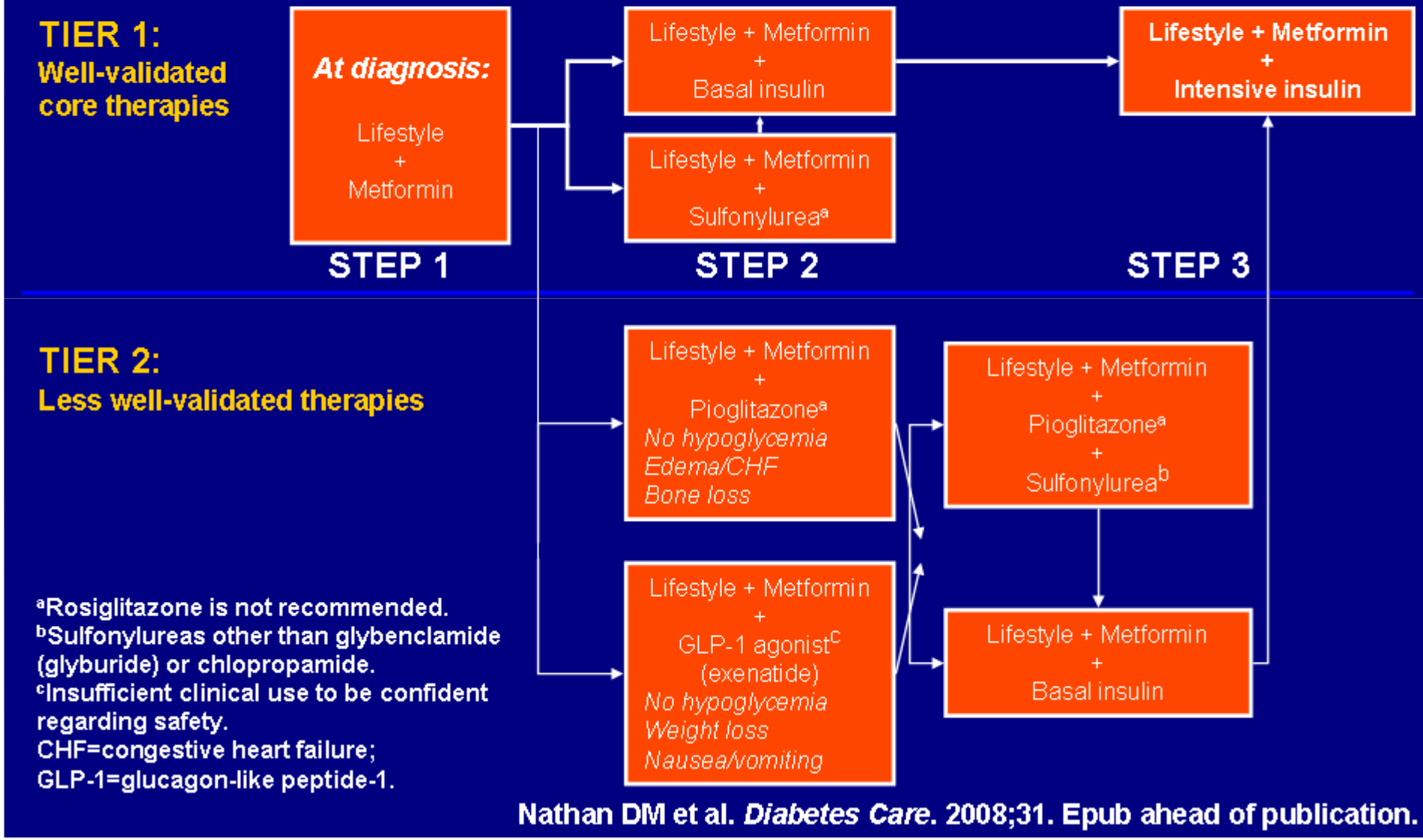
Gli algoritmi terapeutici di AMD: la personalizzazione terapeutica correlata all'autocontrollo glicemico

Antonio Ceriello

Insititut d'Investigacions Biomèdiques
August Pi i Sunyer (IDIBAPS)
Barcelona
Spain

IDIBAPS
Institut
D'Investigacions
Biomèdiques
August Pi i Sunyer

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.

AACE/ACE Diabetes Algorithm *For Glycemic Control*

A1C Goal ≤ 6.5%*

LIFESTYLE MODIFICATION

A1C 6.5 – 7.5%**

Monotherapy

MET	TZD [2]	DPP4 [1]	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 Subcommittee

Cochairpersons:
Helena W. Rodbard, MD, FACP, MACE
Paul S. Jellinger, MD, MACE

Zachary T. Bloomgarden, MD, FACE
Jaime A. Davidson, MD, FACP, MACE
Daniel Einhorn, MD, FACP, FACE
Alan J. Garber, MD, PhD, FACE
James R. Gavin III, MD, PhD
George Grunberger, MD, FACP, FACE
Yehuda Handelsman, MD, FACP, FACE
Edward S. Horton, MD, FACE
Harold Lebovitz, MD, FACE
Philip Levy, MD, MACE
Etie S. Moghissi, MD, FACP, FACE
Stanley S. Schwartz, MD, FACE

* 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

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

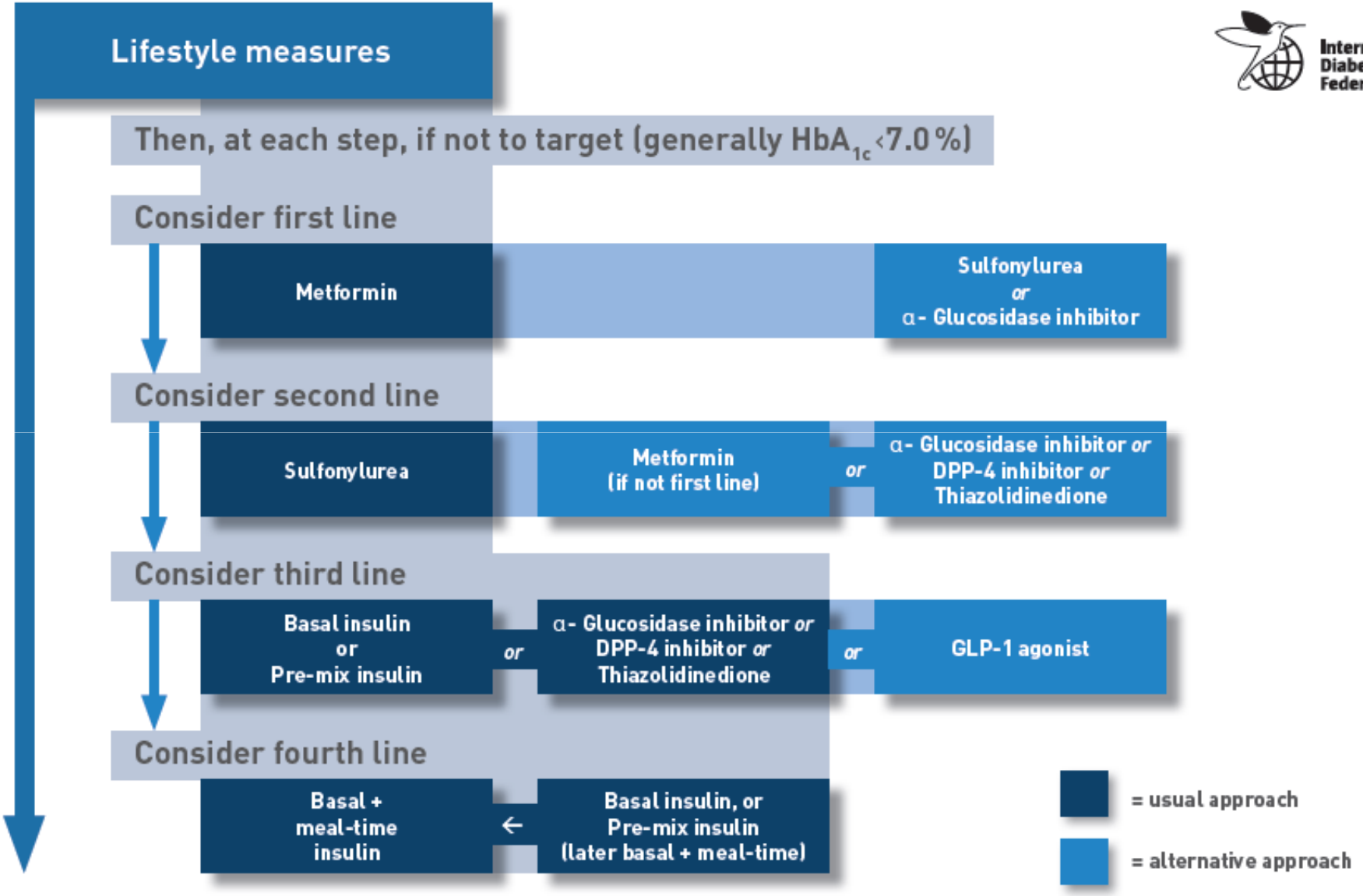
7 Decrease secretagogue by 50% when added to GLP-1 or DPP-4

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

Available at **www.aace.com/pub**

IDF Treatment Algorithm for People with Type 2 Diabetes



Current clinical practice in Diabetes

Current clinical practice in Diabetes

When we do not know what to do….

We create a Guideline

Annals of Internal Medicine | Review

Evaluation of Guideline Recommendations on Oral Medications for Type 2 Diabetes Mellitus

Agreement With Evidence-Based Conclusions*							Evidence Synthesis	
Met Favored as First-Line Agent	Met or TZDs Are Associated With a Lower Risk for Hypoglycemia	Most Medications Cause Similar Reductions in HbA_{1c}†	TZDs Are Associated With Edema and Congestive Heart Failure	Met or Acarbose Is Associated With Weight Maintenance	Concern About Rosiglitazone and Risk for Ischemic Heart Disease	Acarbose Is Associated With GI Adverse Effects	Statement of Balance of Benefits and Harms	Formal Strength of Recommendation

Figure 2. Relationship between the editorial independence and rigor of development domain summary scores, by using the AGREE instrument.

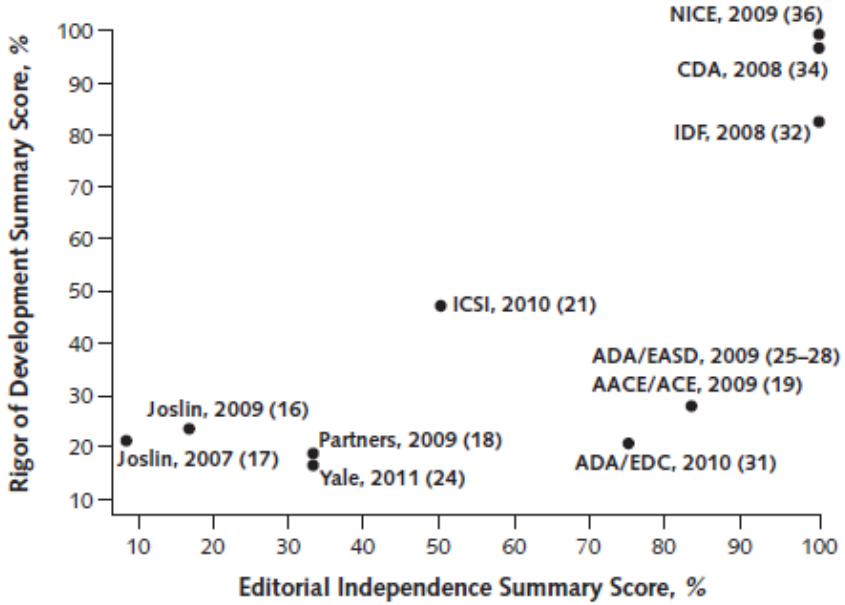
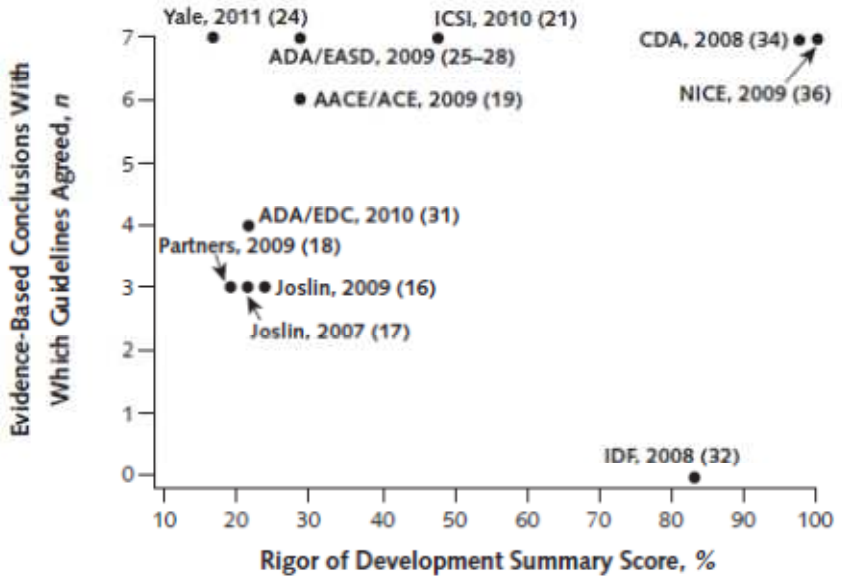


Figure 3. Relationship between rigor of development and editorial independence domain summary scores and consistency of guidelines with evidence-based conclusions.

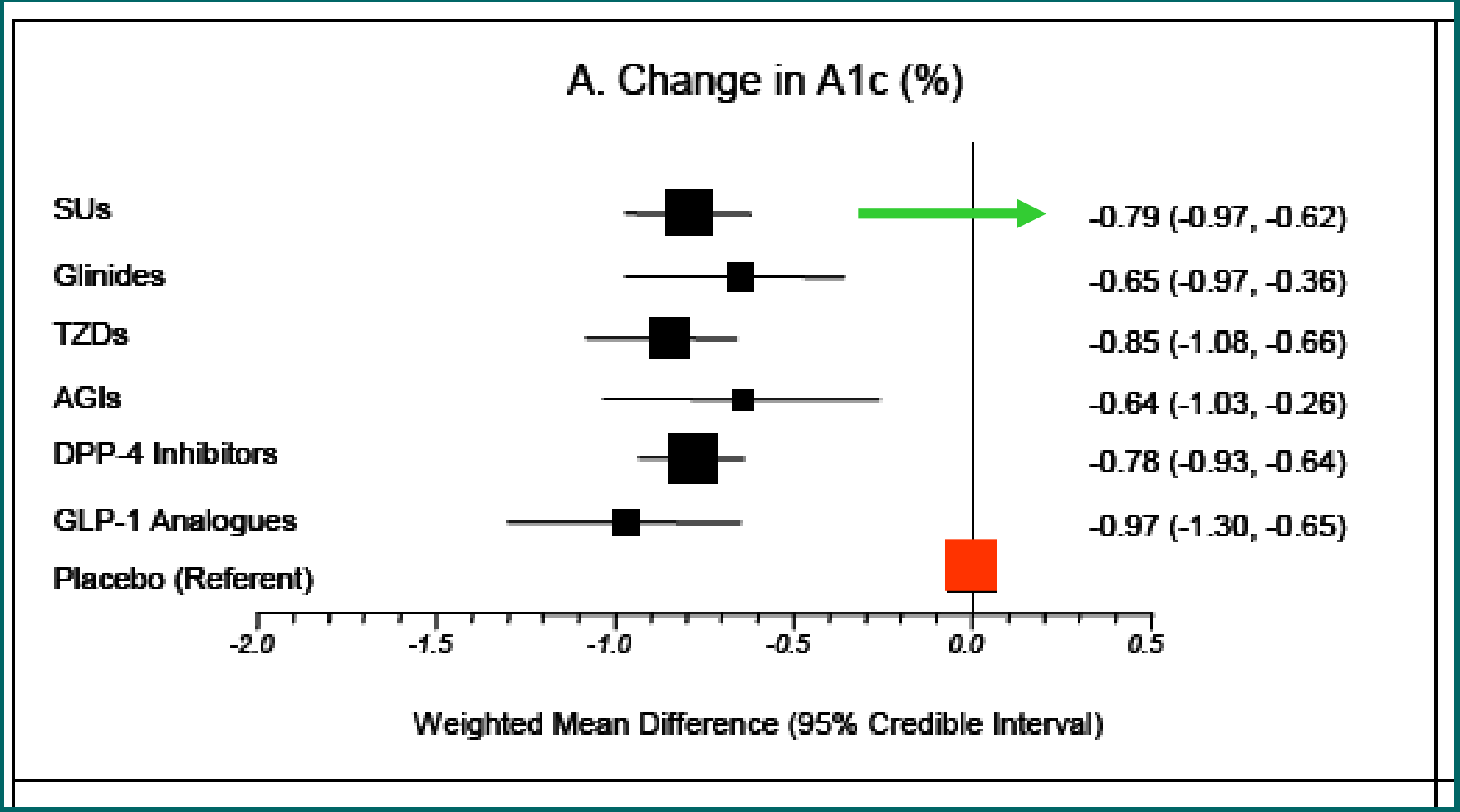


Bennet WL et al. Ann Intern Med 2012

Current Guidelines for T2D treatment

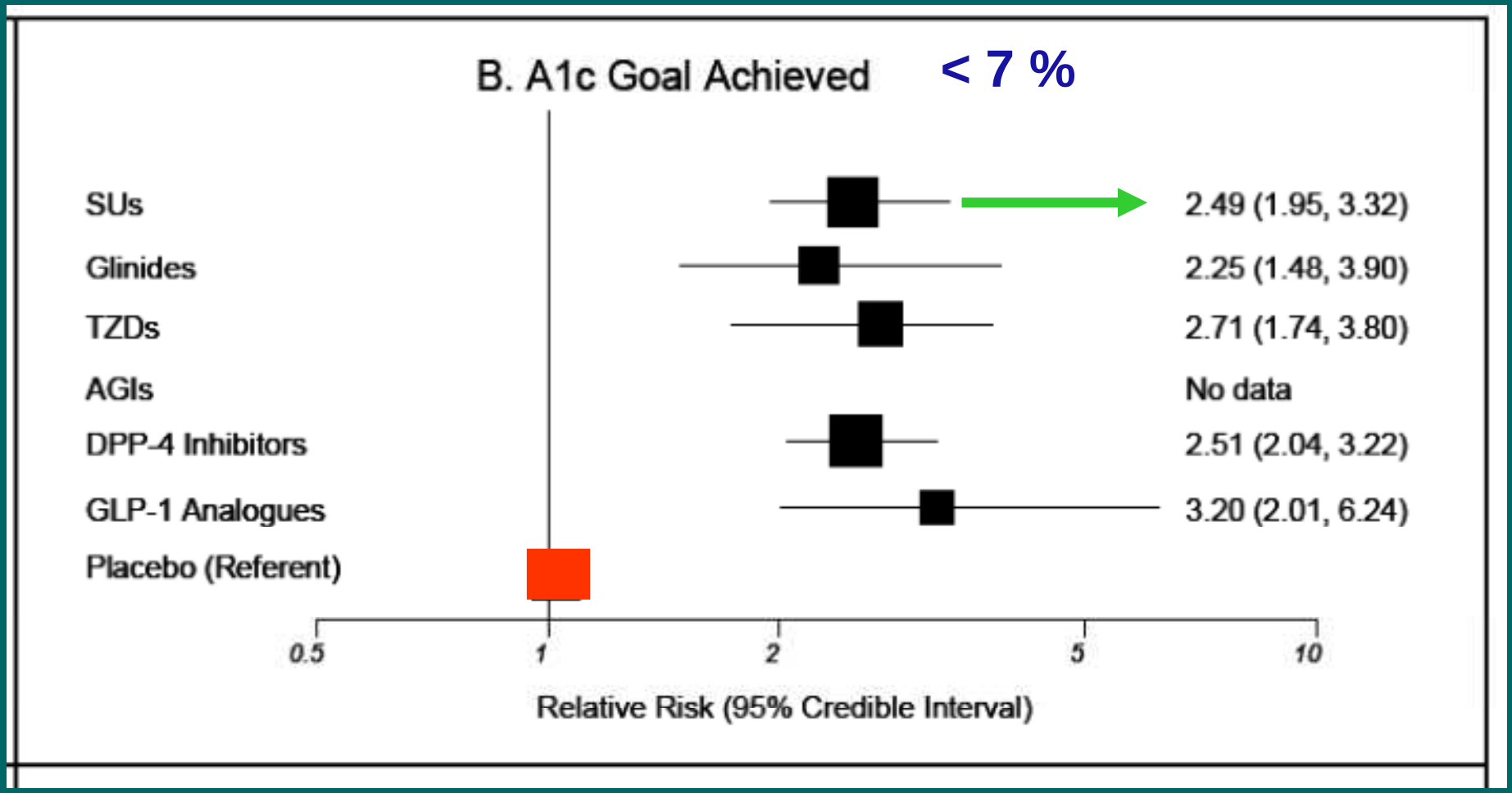
- LSC + Metformin ! Paradigm (T2D = a disease treated using metformin)
- SUs in second line
- Non evidence-based
- Low-cost driven. No matter cost savings in the long-run
- With exceptions, no reference to initial A_{1c}
- In general, IGNORES the stage of the disease
- Non aimed to correct pathophysiological defects or CV risk factors
- Just A_{1c} driven
- IGNORE the needs of individual…

Effects of Non-insulin antidiabetic drugs added to Metformin therapy on glycemic control, weight gain and hypoglycemia in T2D. Pungh et a. JAMA 2010



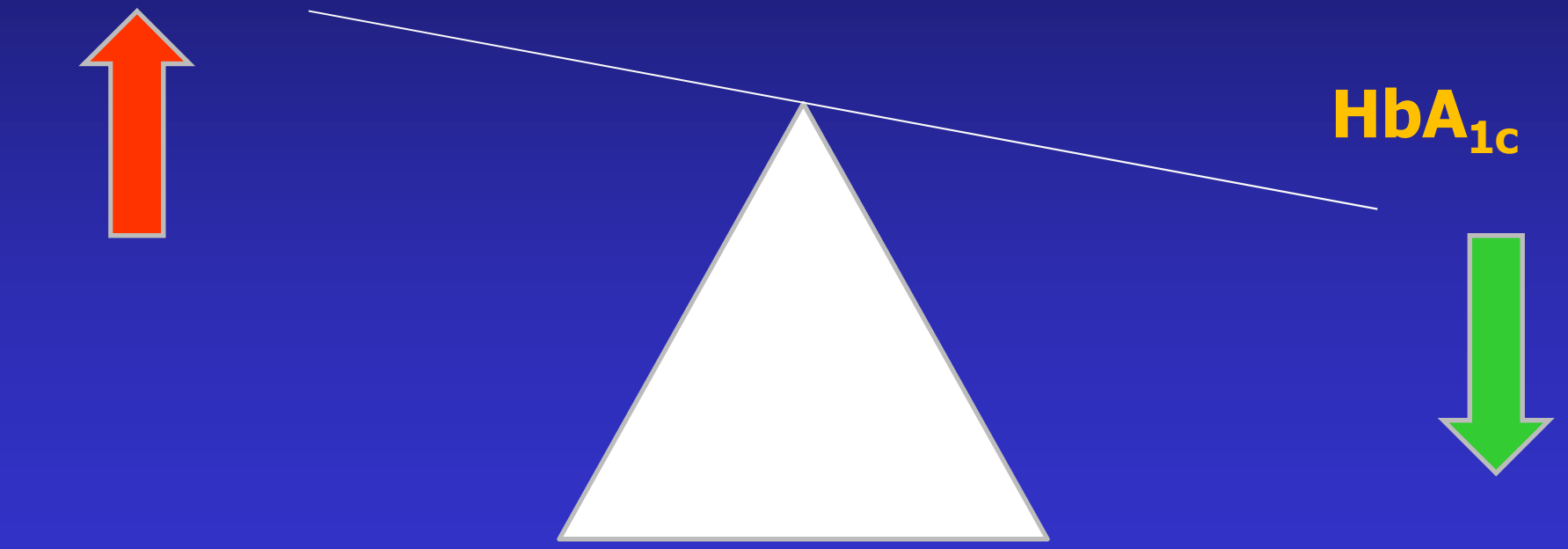
Results of Mixed Treatment Comparison Meta-analysis Presented as Forest Plots

Effects of Non-insulin antidiabetic drugs added to Metformin therapy on glycemic control, weight gain and hypoglycemia in T2D. Pungh et a. JAMA 2010

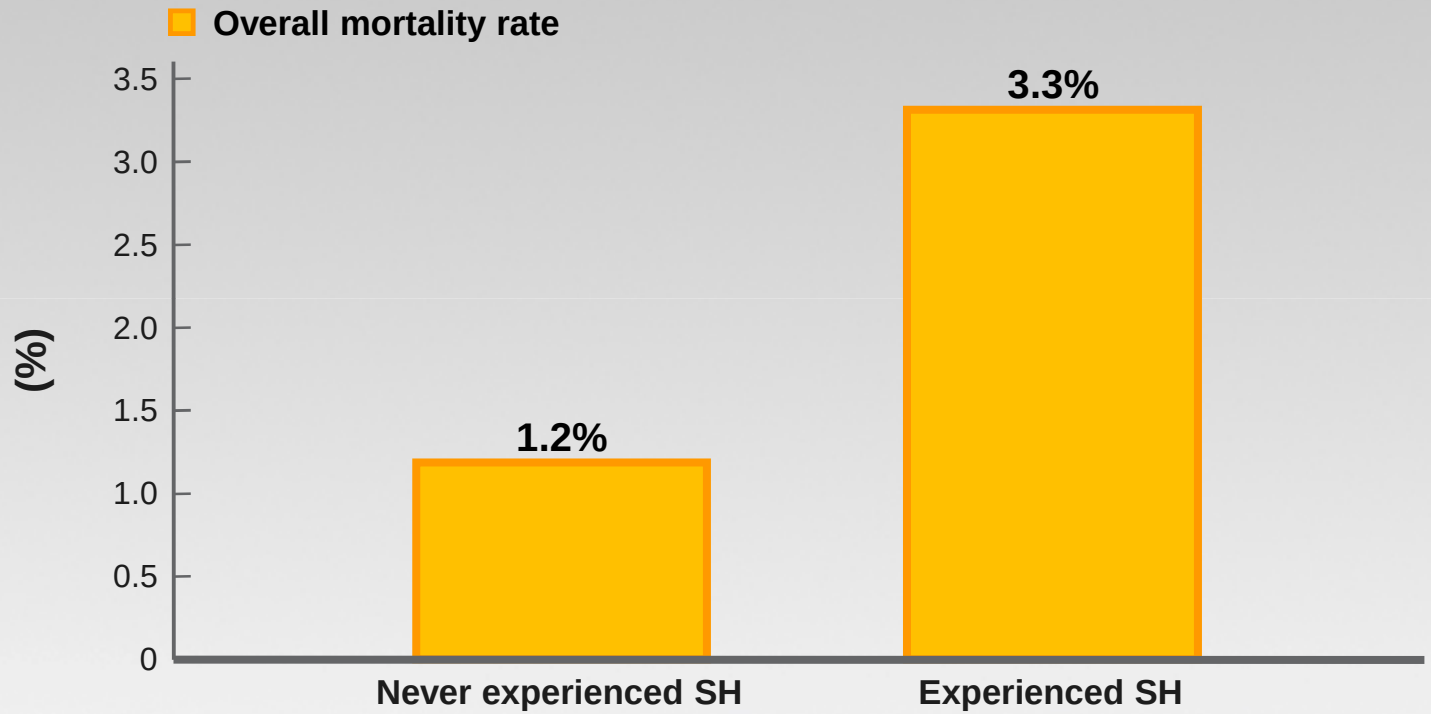


Results of Mixed Treatment Comparison Meta-analysis Presented as Forest Plots

The challenge of blood glucose control

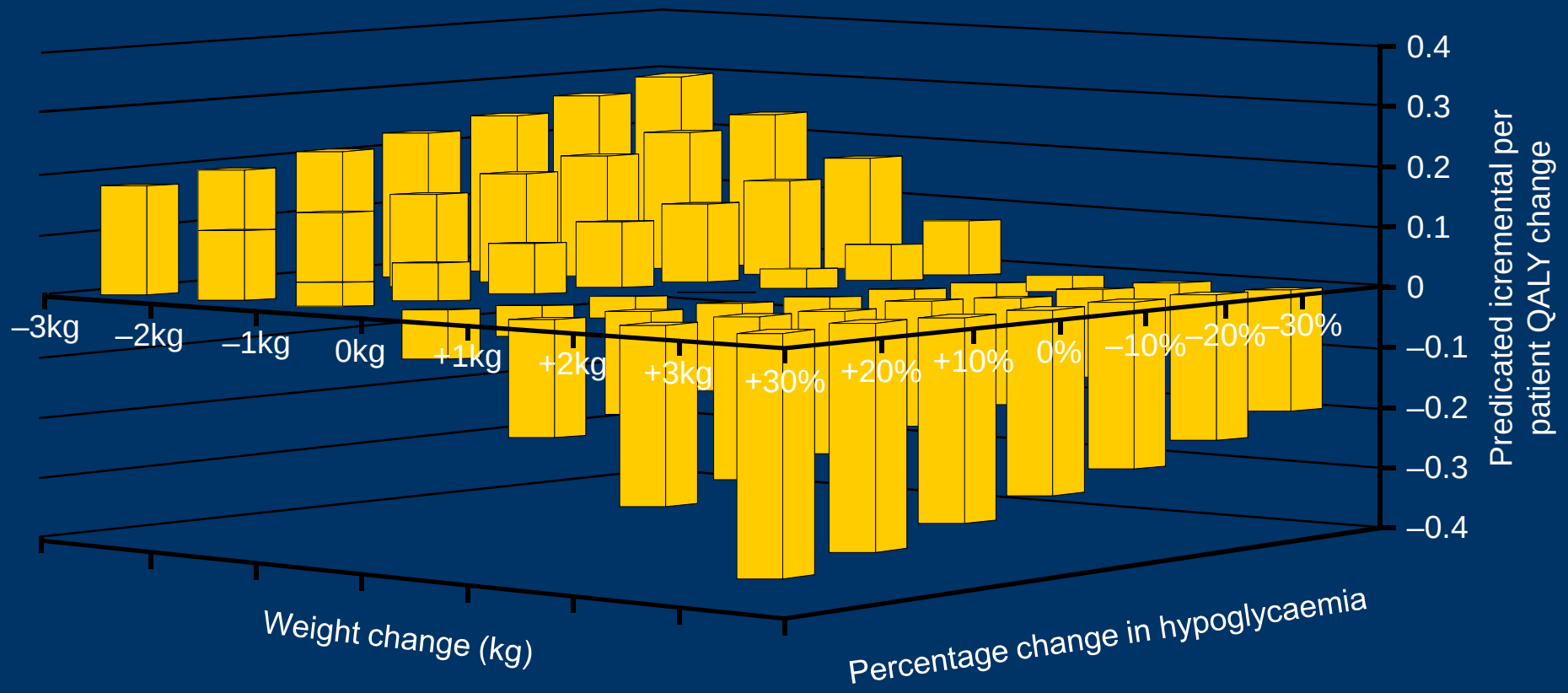


Hypoglycaemia and mortality – The ACCORD experience



Bonds DE et al. BMJ 2010

Relationship between weight gain, hypoglycaemia and quality of life

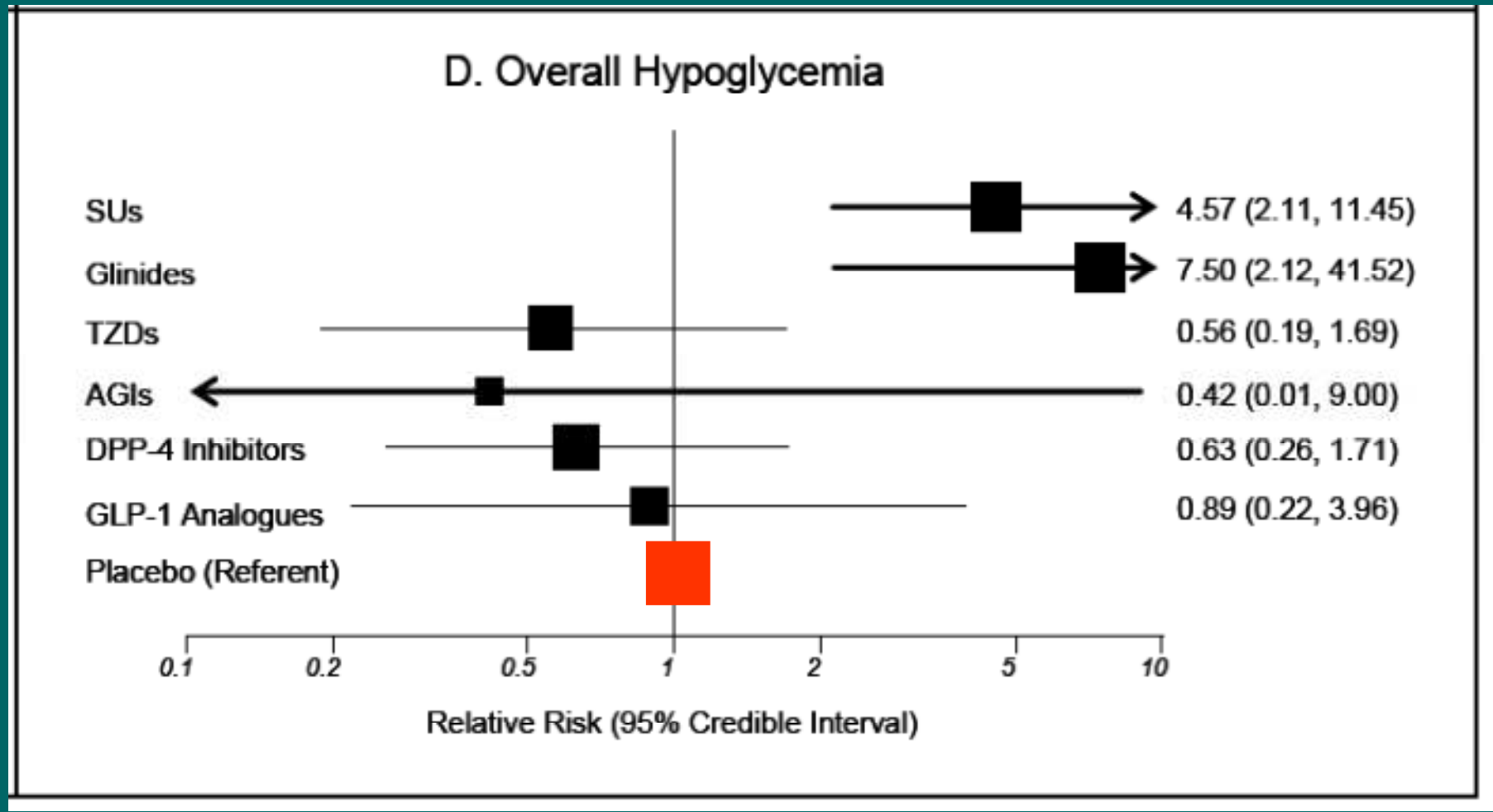


The graph illustrates that the QALY decrement associated with an increase in weight and hypoglycaemia by approximately 3 kg and 30%, respectively, will offset the QALY gain associated with a 1% reduction in HbA_{1c}

QALY: quality-adjusted life year

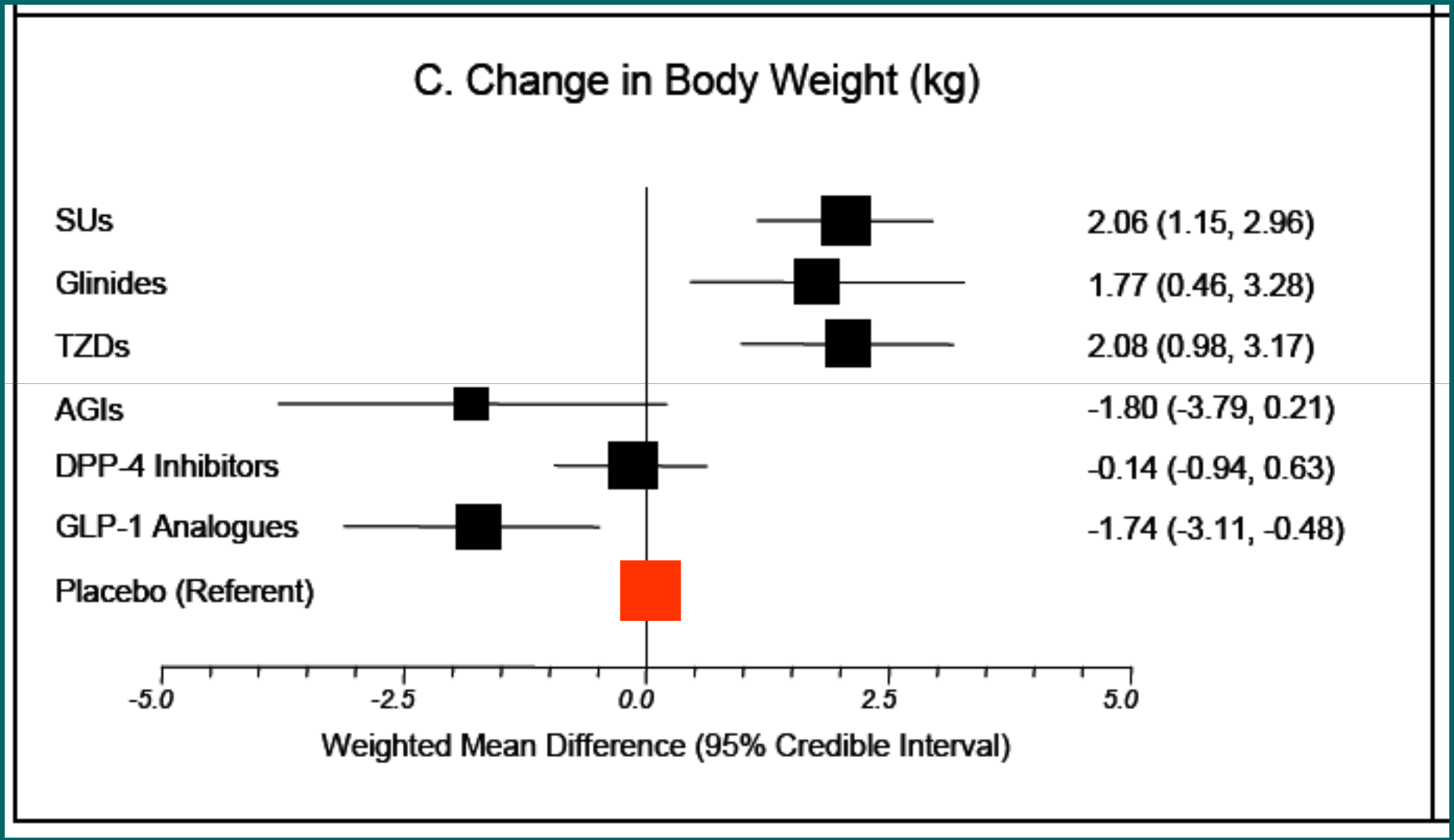
McEwan et al. Diabetes Obes Metab 2010;12:431–6

Effects of Non-insulin antidiabetic drugs added to Metformin therapy on glycemic control, weight gain and hypoglycemia in T2D. Pungh et a. JAMA 2010



Results of Mixed Treatment Comparison Meta-analysis Presented as Forest Plots

Effects of Non-insulin antidiabetic drugs added to Metformin therapy on glycemic control, weight gain and hypoglycemia in T2D. Pungh et a. JAMA 2010



Results of Mixed Treatment Comparison Meta-analysis Presented as Forest Plots

Translating clinical trials

Into

Clinical Practice

ACCORD

ADVANCE

VADT

?

STENO-2

?

ADOPT

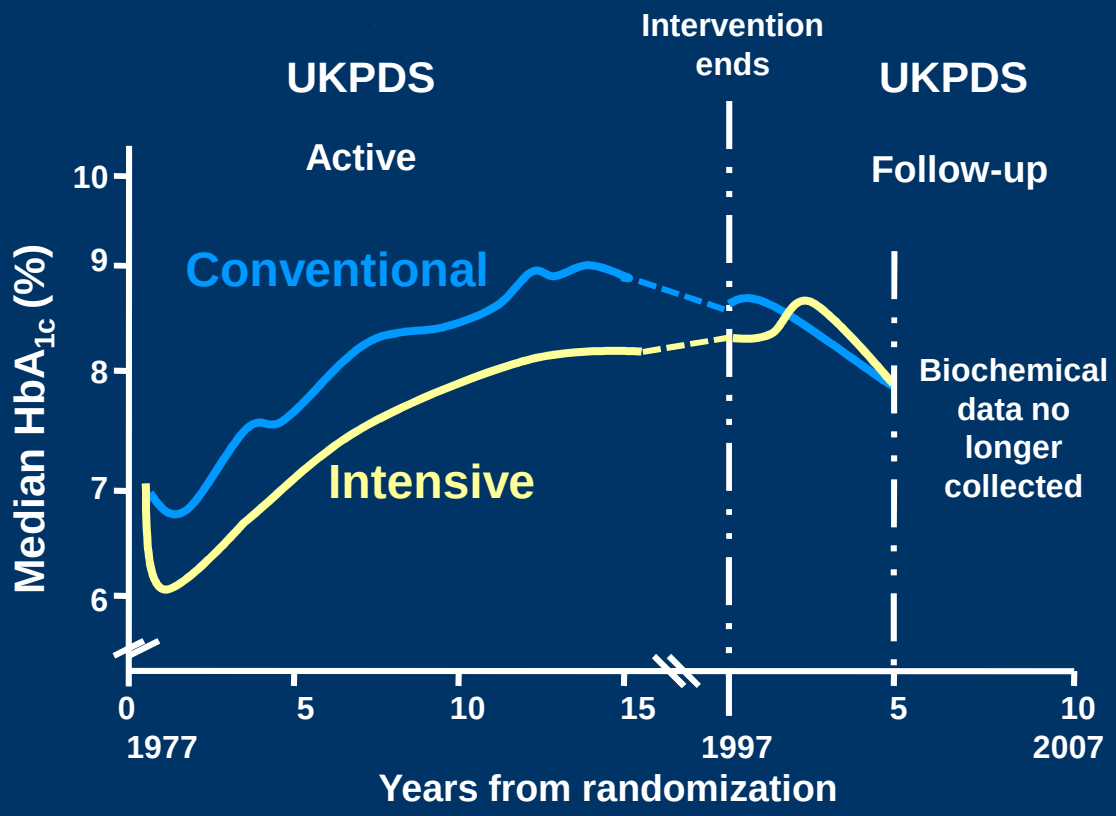
UKPDS

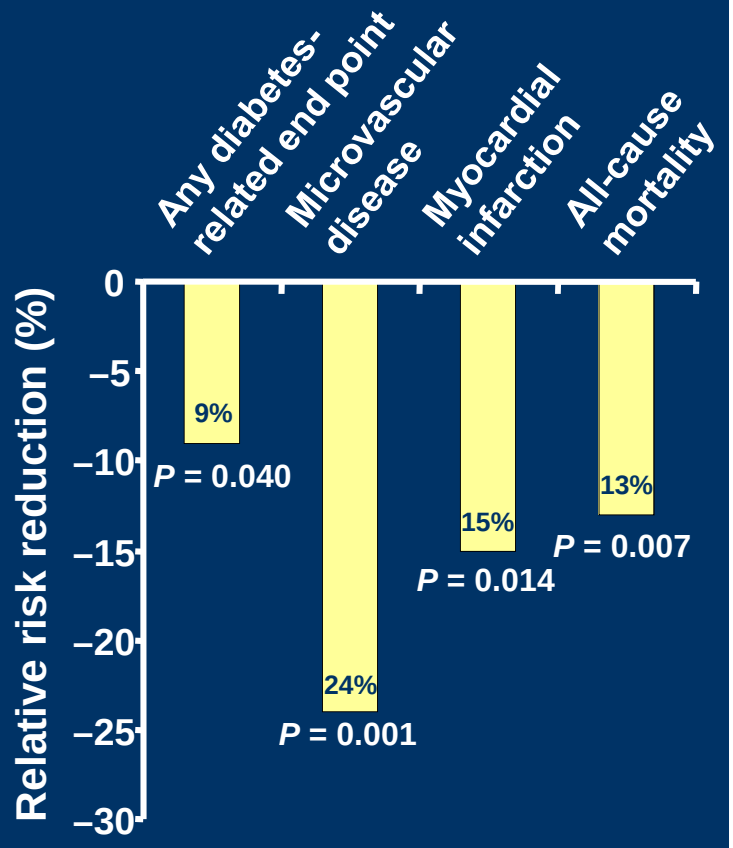
?

Lot's RCTs

On drugs

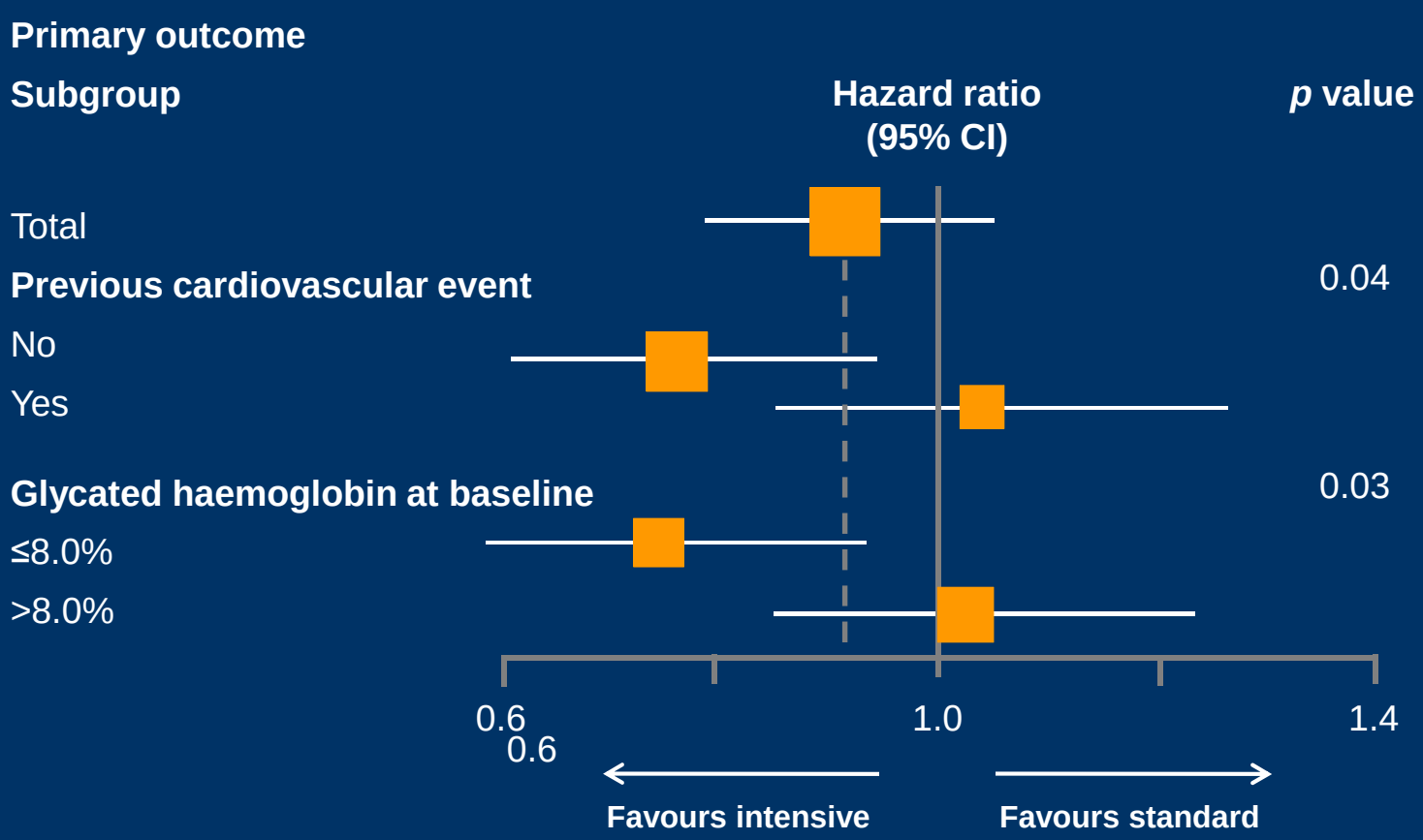
UKPDS: long-term follow-up and legacy effect





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.

ACCORD: Intensive Glucose Control Beneficial in Patients with No Previous CVD or HbA1c <8%



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

ACCORD Study Group. *N Engl J Med* 2008;358:2545–2559.

Defining metabolic memory

JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

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

The "Metabolic Memory": Is More Than Just Tight Glucose Control Necessary to Prevent Diabetic Complications?

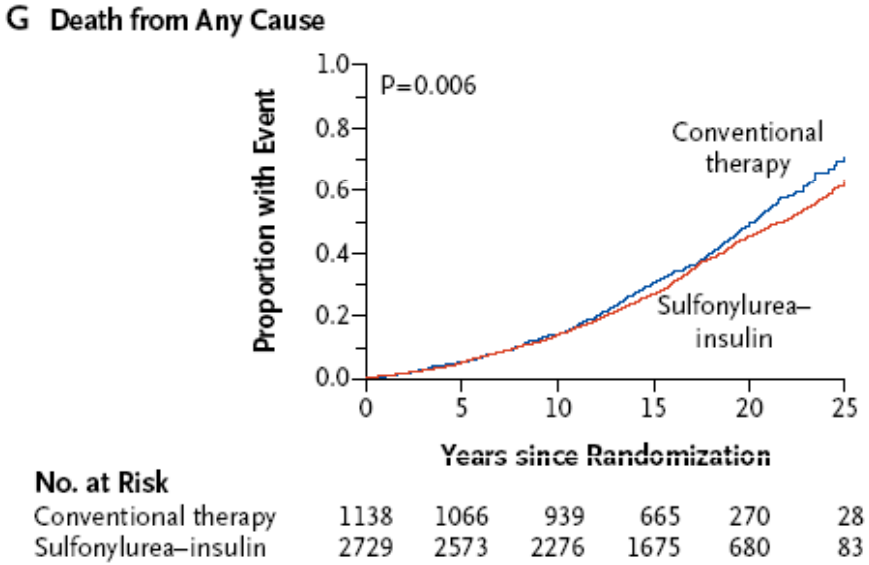
J Clin. Endocrinol. Metab. 2009 94:410-415

- *"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"

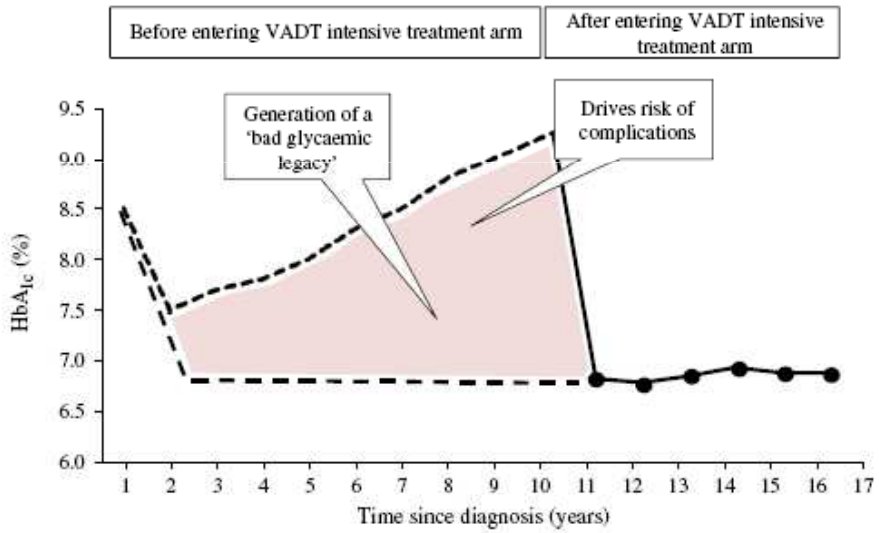
The Metabolic Memory

- UKPDS



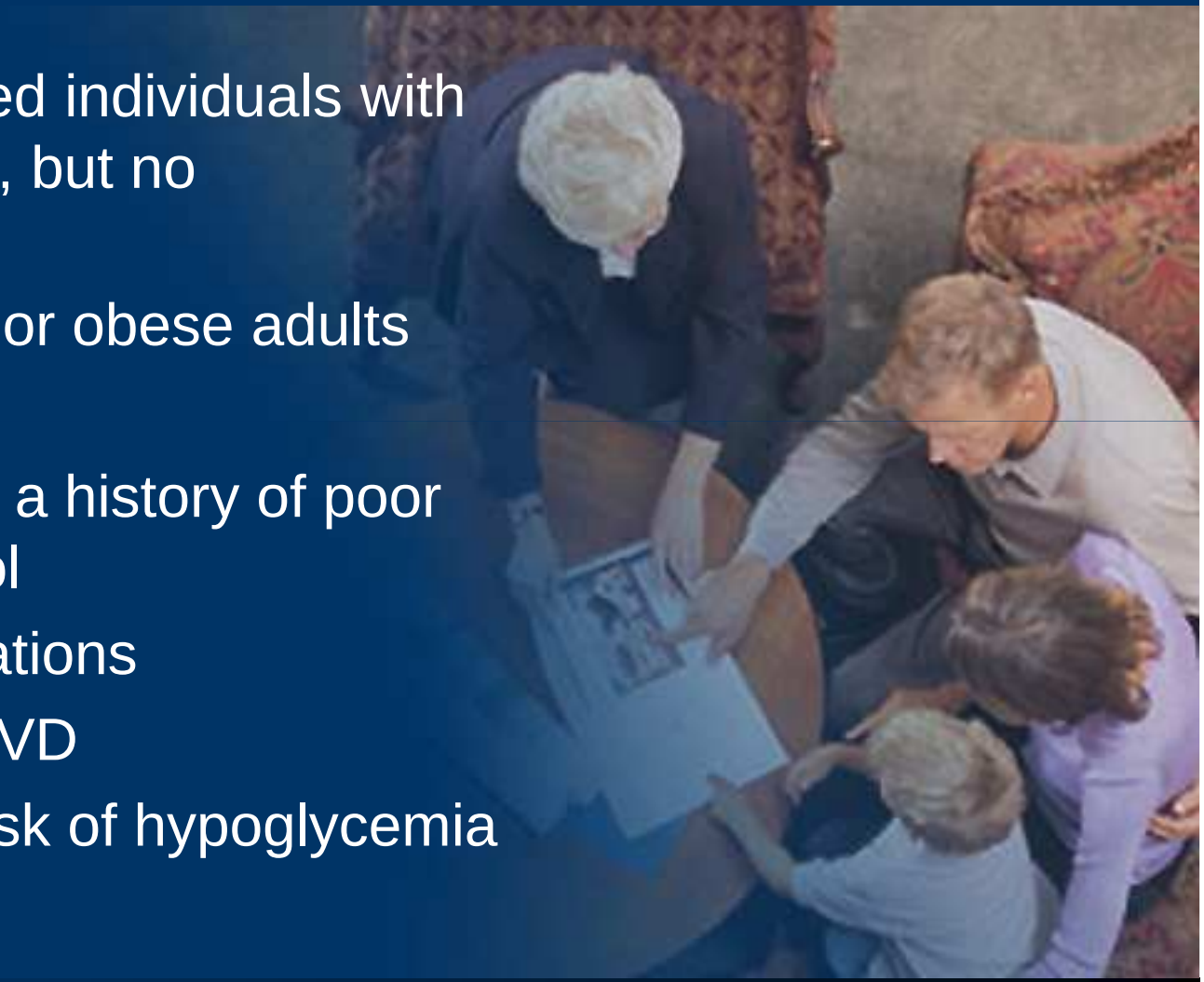
Holman R et al. N Engl J Med. 2008 ;359: 1577-89

- VADT



Del Prato S, Diabetologia 2009; 52:1219–1226

Patient groups requiring special consideration

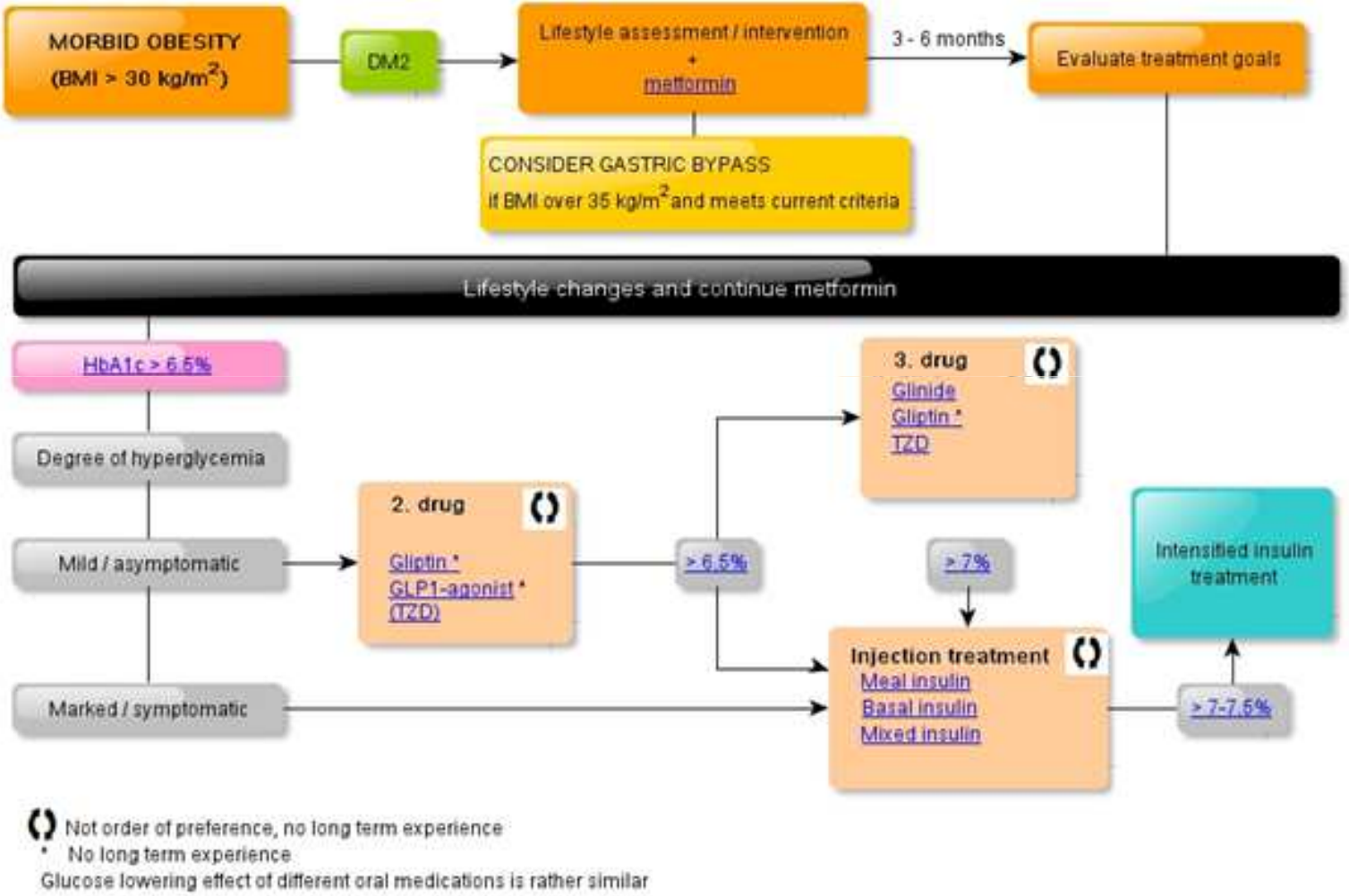


- Newly diagnosed individuals with type 2 diabetes, but no complications
  - Overweight or obese adults
  - Lean adults
- Individuals with a history of poor glycemic control
  - No complications
  - History of CVD
- Individuals at risk of hypoglycemia

Del Prato S, *et al*. *Int J Clin Pract* 2010.

Choose the main feature of your patient

Early diabetes | Chronic diabetes > 10 yrs | Morbid obesity | Elderly patient | Transport occupation | Impaired kidney function



( ) Not order of preference, no long term experience

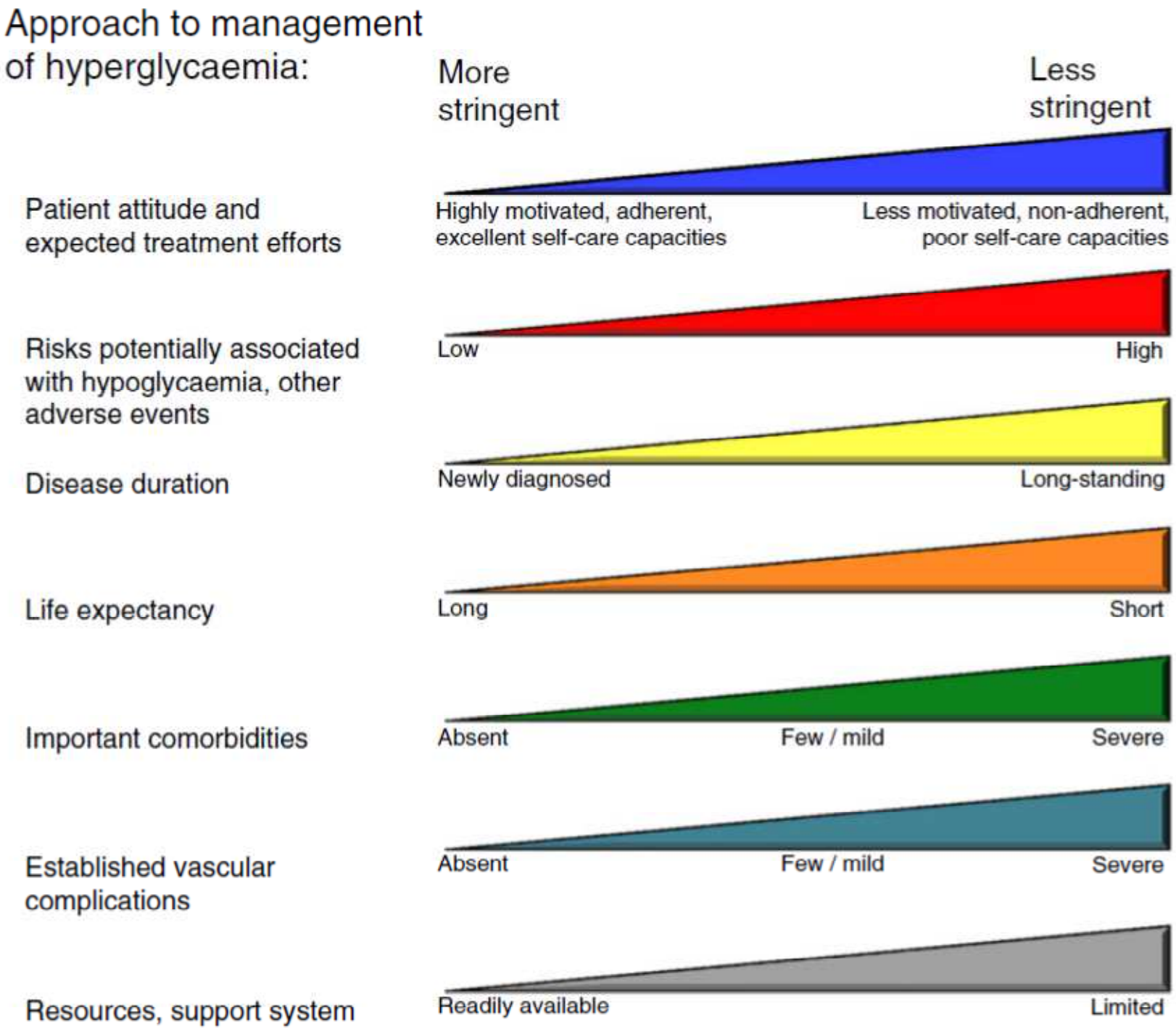
* No long term experience

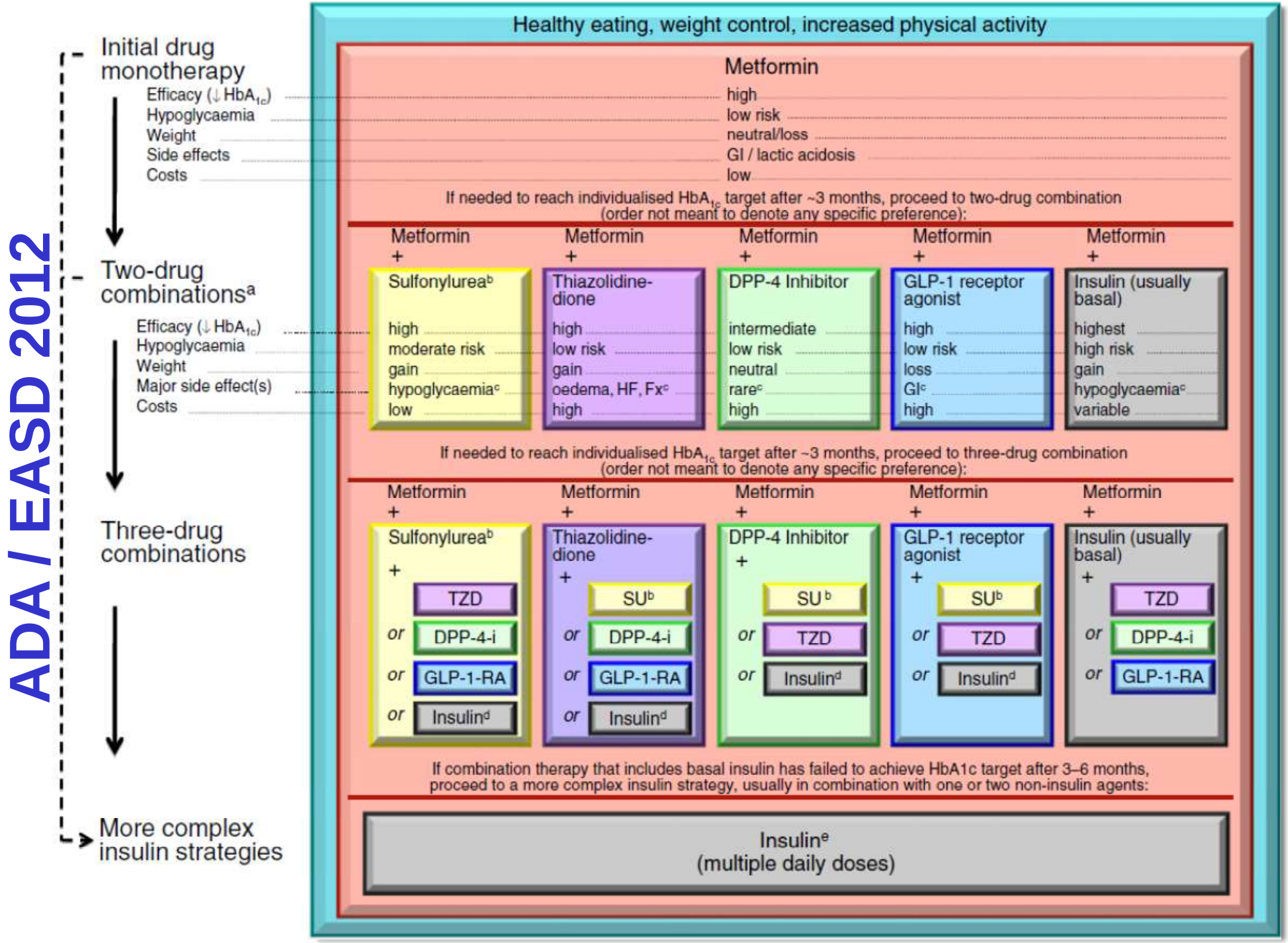
Glucose lowering effect of different oral medications is rather similar

ADA/EASD 2012 Key points

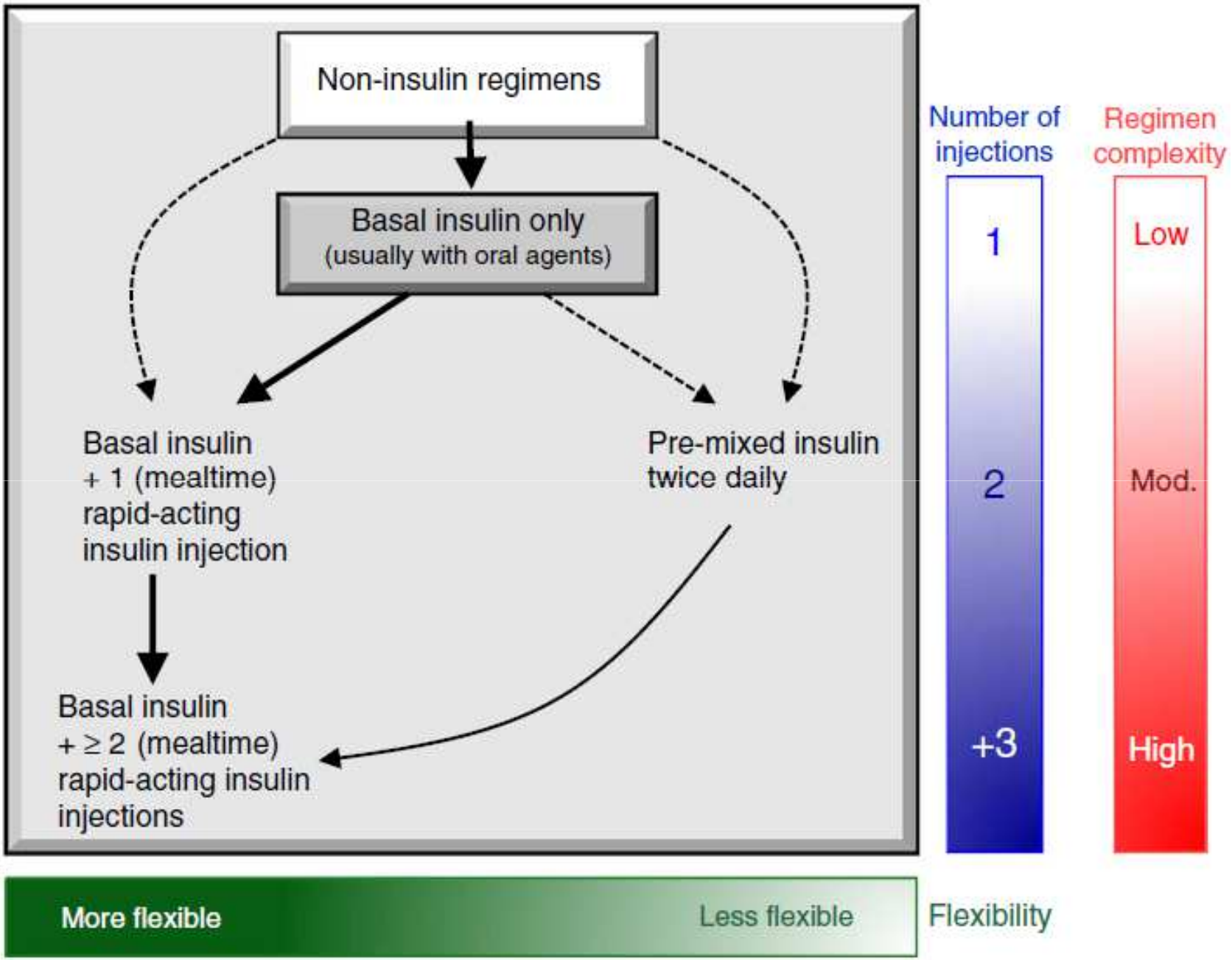
- Glycaemic targets and glucose-lowering therapies must be individualised
- Diet, exercise and education remain the foundation of any type 2 diabetes treatment programme
- Unless there are prevalent contraindications, metformin is the optimal first-line drug
- After metformin, there are limited data to guide us. Combination therapy with an additional 1–2 oral or injectable agents is reasonable, aiming to minimise side effects where possible
- Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control
- All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs and values
- Comprehensive cardiovascular risk reduction must be a Implementation strategies

ADA / EASD 2012




ADA / EASD 2012
Initial drug monotherapy
Efficacy (↓ HbA1c)
Hypoglycaemia
Weight
Side effects
Costs
Two-drug combinations[a]
Efficacy (↓ HbA1c)
Hypoglycaemia
Weight
Major side effect(s)
Costs
Three-drug combinations
More complex insulin strategies
Healthy eating, weight control, increased physical activity
Metformin
high
low risk
neutral/loss
GI / lactic acidosis
low
If needed to reach individualised 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
hypoglycaemia[c]
low
Metformin + Thiazolidine-dione
high
low risk
gain
oedema, HF, Fx[c]
high
Metformin + DPP-4 Inhibitor
intermediate
low risk
neutral
rare[c]
high
Metformin + GLP-1 receptor agonist
high
low risk
loss
GI[c]
high
Metformin + Insulin (usually basal)
highest
high risk
gain
hypoglycaemia[c]
variable
If needed to reach individualised HbA1c target after ~3 months, proceed to three-drug combination (order not meant to denote any specific preference):
Metformin + Sulfonylurea[b] + TZD or DPP-4-i or GLP-1-RA or Insulin[d]
Metformin + Thiazolidine-dione + SU[b] or DPP-4-i or GLP-1-RA or Insulin[d]
Metformin + DPP-4 Inhibitor + SU[b] or TZD or Insulin[d]
Metformin + GLP-1 receptor agonist + SU[b] or TZD or Insulin[d]
Metformin + Insulin (usually basal) + TZD or DPP-4-i or GLP-1-RA
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



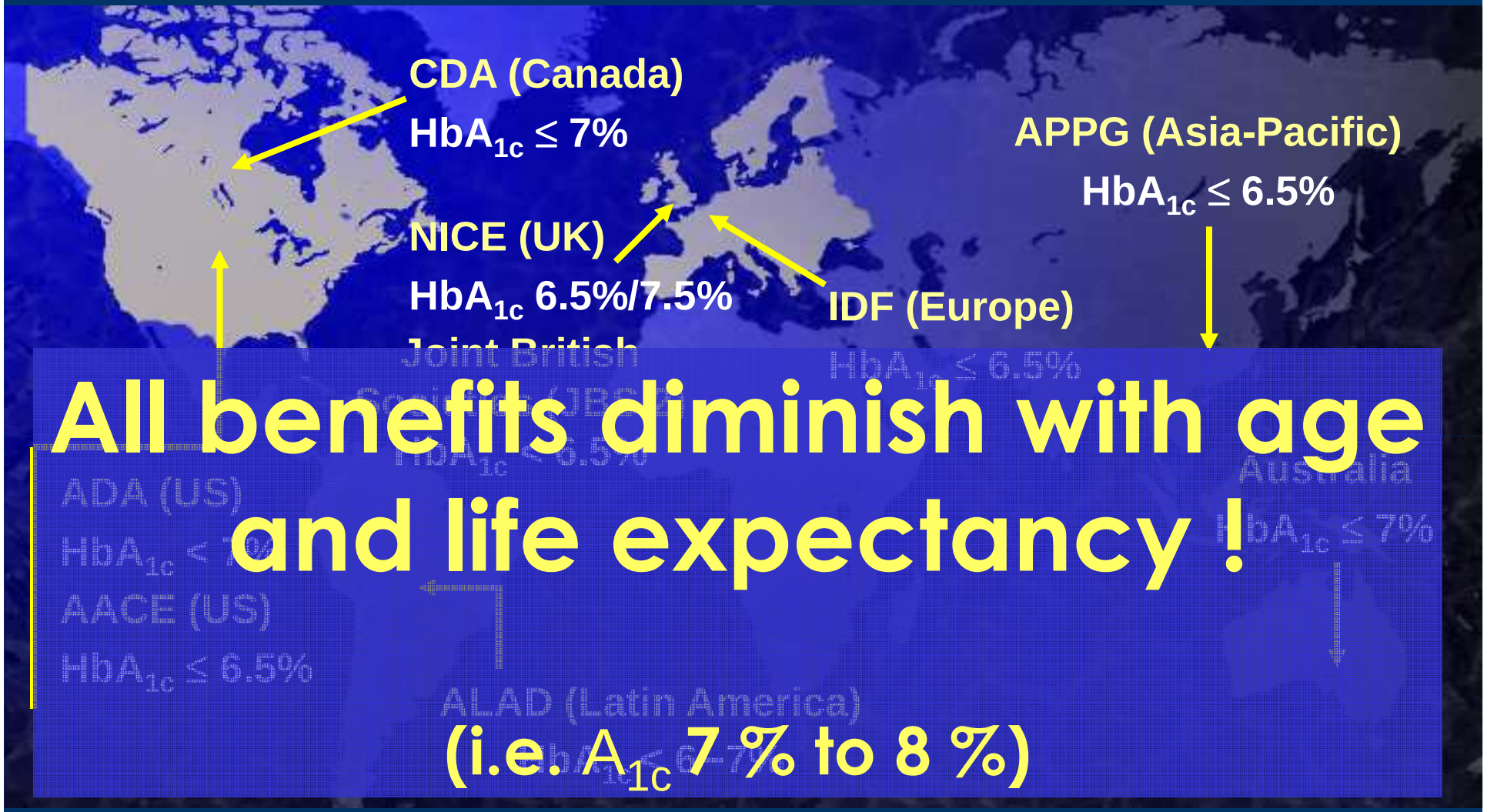
Atypical Guidelines for individualising T2D treatment

- Newly-diagnosed - History of DT2 – Previous glycemic control (pathophysiology, phenotype, glycemic profile…) ?
  - Address the underlying pathophysiology of diabetes, including the treatment of β-cell dysfunction and insulin resistance

Atypical Guidelines for individualising T2D treatment

- Newly-diagnosed - History of DT2 – Previous glycemic control ?
- What is our A_{1c} target ?

HbA_{1c} targets generally 6.5–7% when safe and appropriate



All benefits diminish with age and life expectancy !

(i.e. A_{1c} 7 % to 8 %)

ADA. *Diabetes Care* 2009; **32**(Suppl 1)**:**S13–S61; American Association of Clinical Endocrinologists. *Endocr Pract* 2007; **13**(Suppl. 1)**:**1–68. IDF. Global guideline for type 2 diabetes, *IDF* 2005. Available at: http://www.idf.org/Global_guideline. JBS2. *Heart* 2005; **91**(Suppl. V)**:**1–52. European Diabetes Policy Group. *Diabet Med* 1999; **16:**716–730. CDA. *Can J Diabetes* 2008; **32**(Suppl. 1)**:**S1–S201. NICE. 2009. Available at: http://www.nice.org.uk/nicemedia/pdf/CG87ShortGuideline.pdf; ALAD. *Rev Assoc Lat Diab* 2000; Suppl. 1. Asian-Pacific Policy Group. Practical Targets and Treatments (3rd Edn). Available at: http://www.idf.org/webdata/docs/T2D_practical_tt.pdf. NSW Health Department. The Principles of Diabetes Care and Guidelines for the Clinical Management of Diabetes Mellitus in Adults. NSW Health Department 1996.

Atypical Guidelines for individualising T2D treatment

- Newly-diagnosed - History of DT2 – Previous glycemic control, phenotype & background ?
- What is our A_{1c} target ?

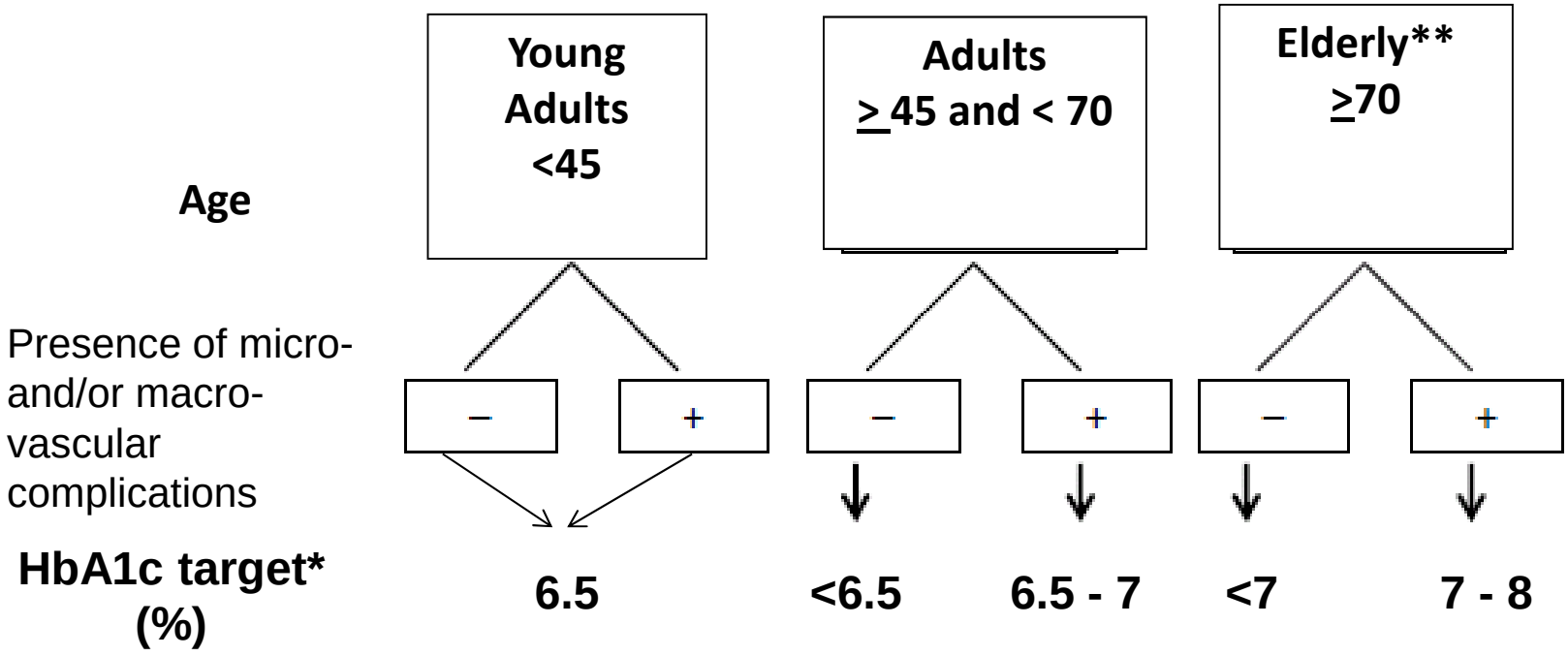
"PERSONALIZING TREATMENT IN TYPE 2 DIABETES: A SMBG INCLUSIVE INNOVATIVE APPROACH"

AUTHORS

Antonio Ceriello, Marco Gallo, Vincenzo Armentano, Gabriele Perriello, Sandro Gentile, Alberto De Micheli.

On behalf of Associazione Medici Diabetologi (AMD)

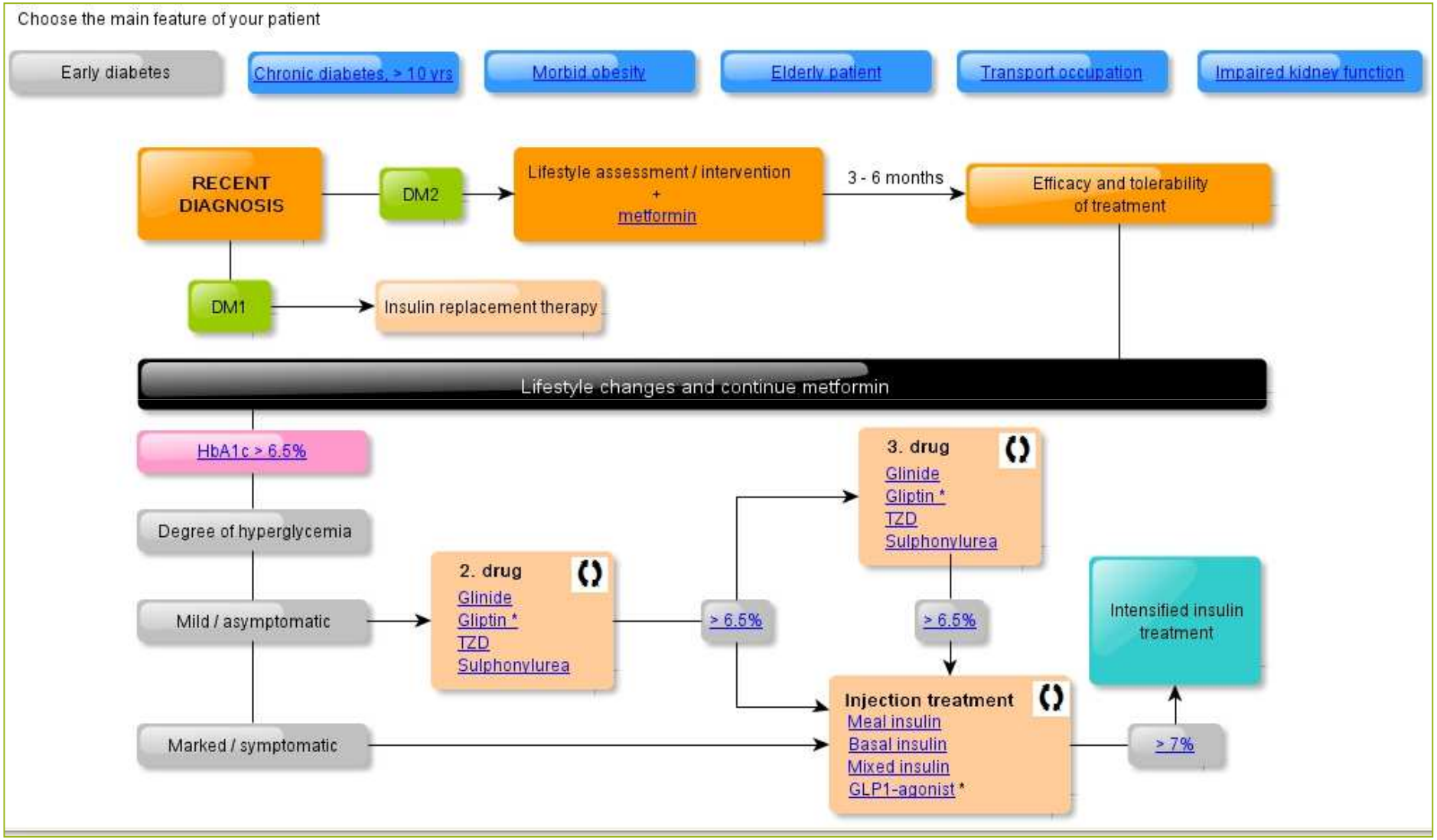
Diabetes Technol Therap, 2012;14:373-8



* The HbA1c target values proposed are intended as safe objectives, limiting the risk of hypoglycaemia

** Carefully evaluate glomerular filtration rate (GFR), potential hypoglycaemia risks (with particular care in the use of sulfonylureas or glinides), and nutritional status

Finnish Guidelines



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

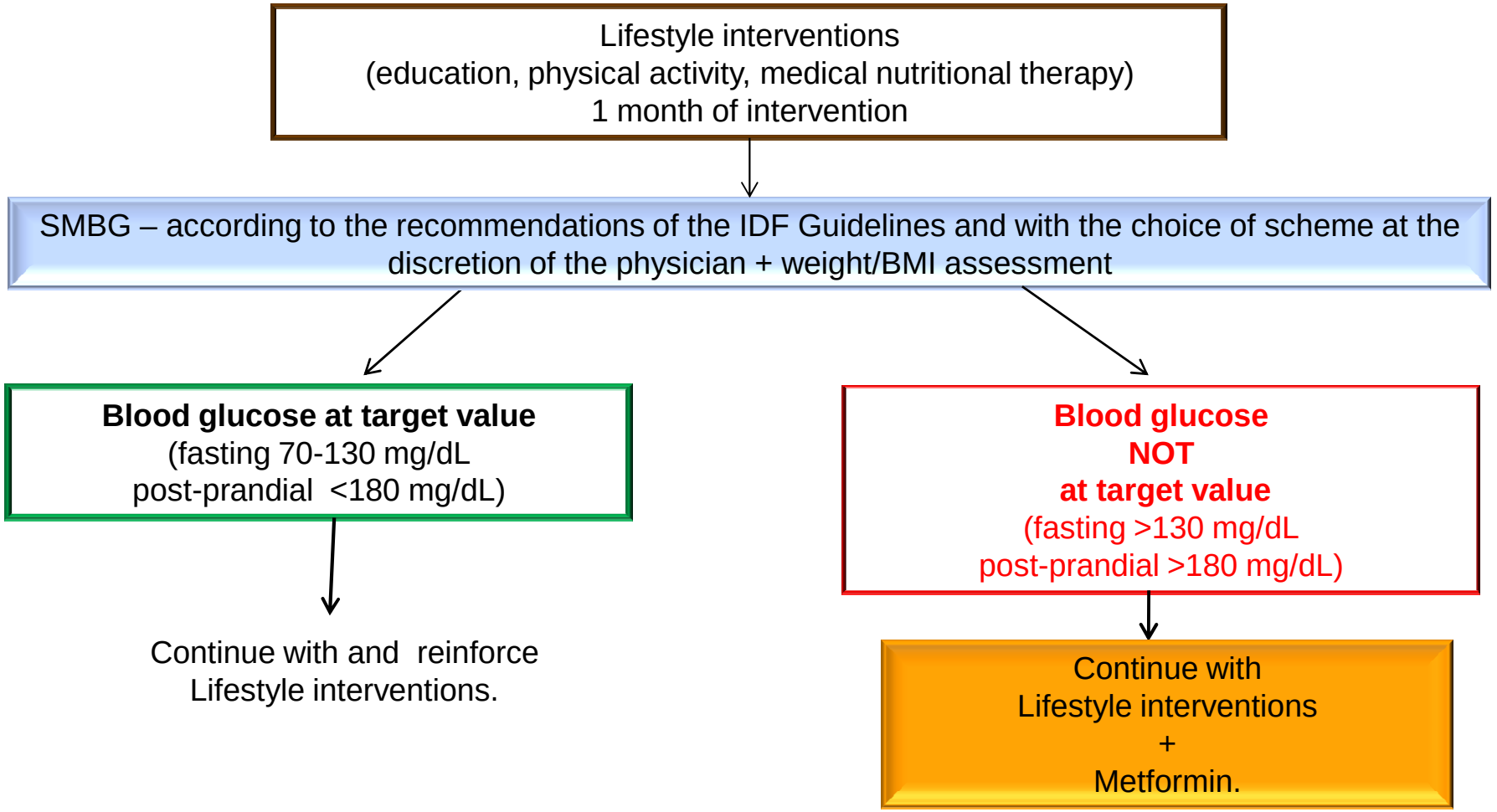
1. Nathan DM, *et al. Diabetes Care* 32(1), 193-203 (2009)
2. AMD-SID. Standard italiani per la cura del diabete mellito 2009-2010
3. www.infodiabetes.it/standard_di_cura/2010_linee_guida.pdf
4. www.siditalia.it/documenti/2010_linee_guida.pdf
5. Duran A, Journal of Diabetes 2 (2010) 203–211.

Model self-monitoring plans

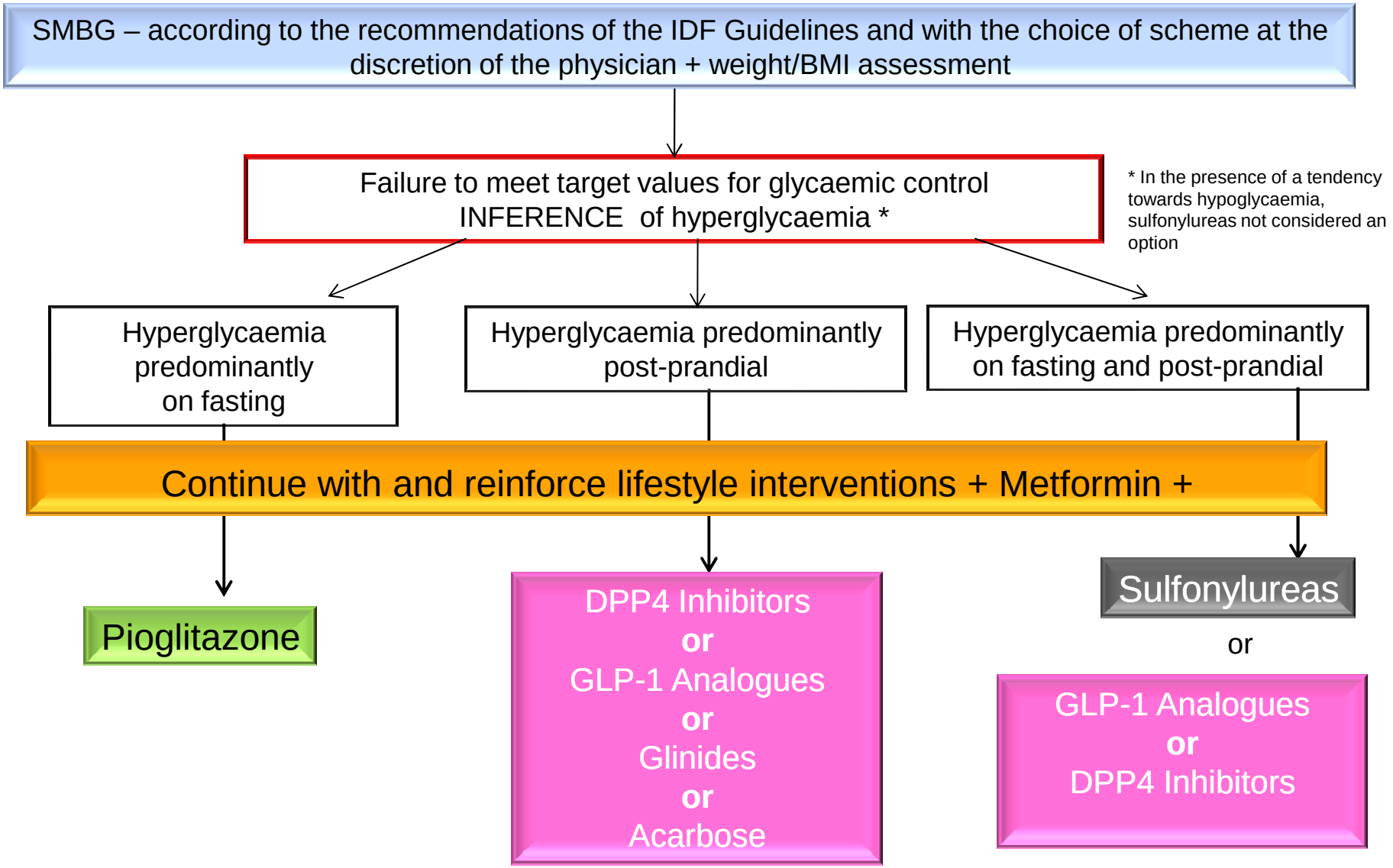
Staggered plan

	Before breakfast	After breakfast	Before lunch	After lunch	Before dinner	After dinner	Bedtime
Monday	X	X					
Tuesday			X	X			
Wednesday					X	X	
Thursday	X	X					
Friday			X	X			
Saturday					X	X	
Sunday	X	X					

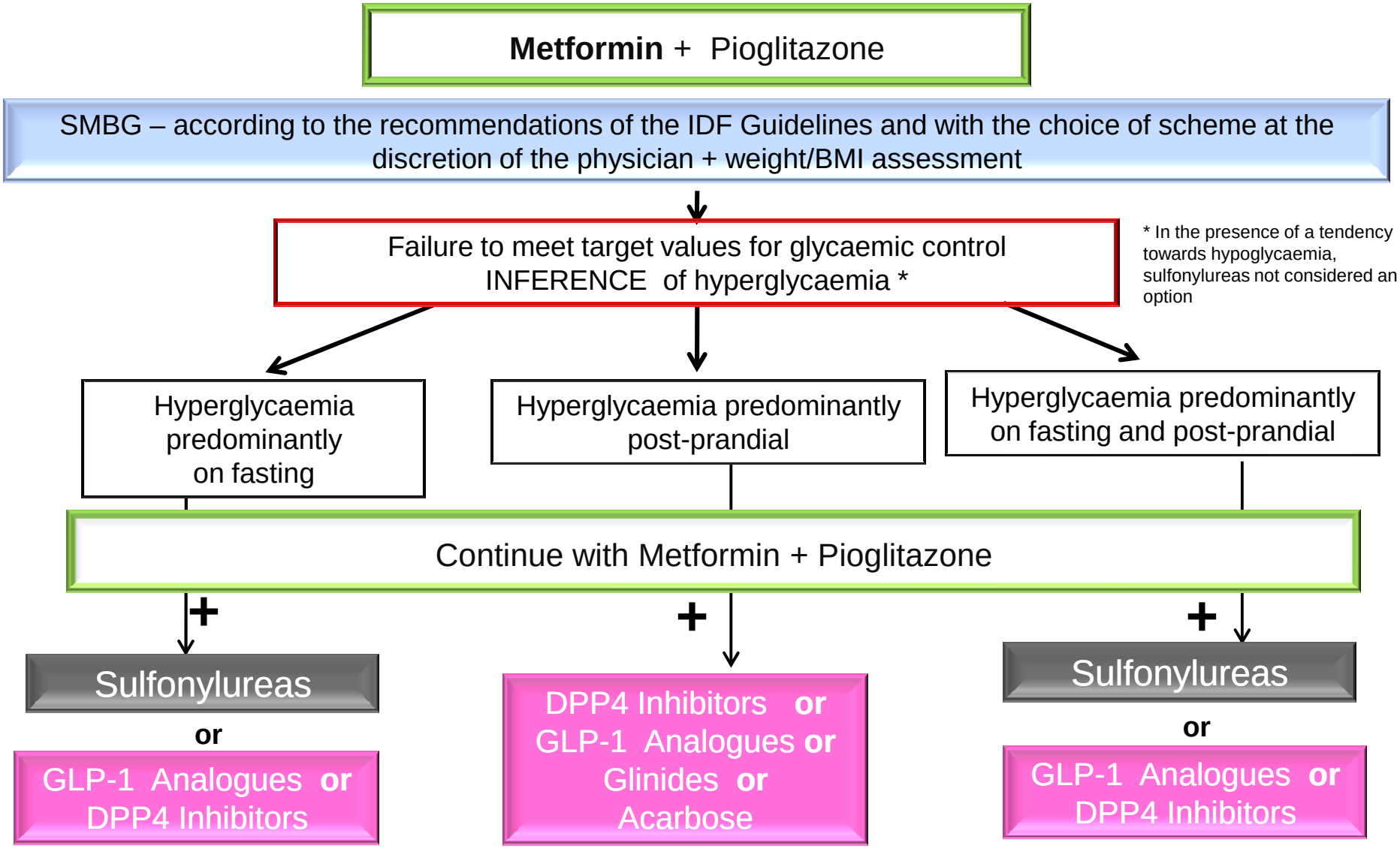
Algorithm B: Flowchart B1



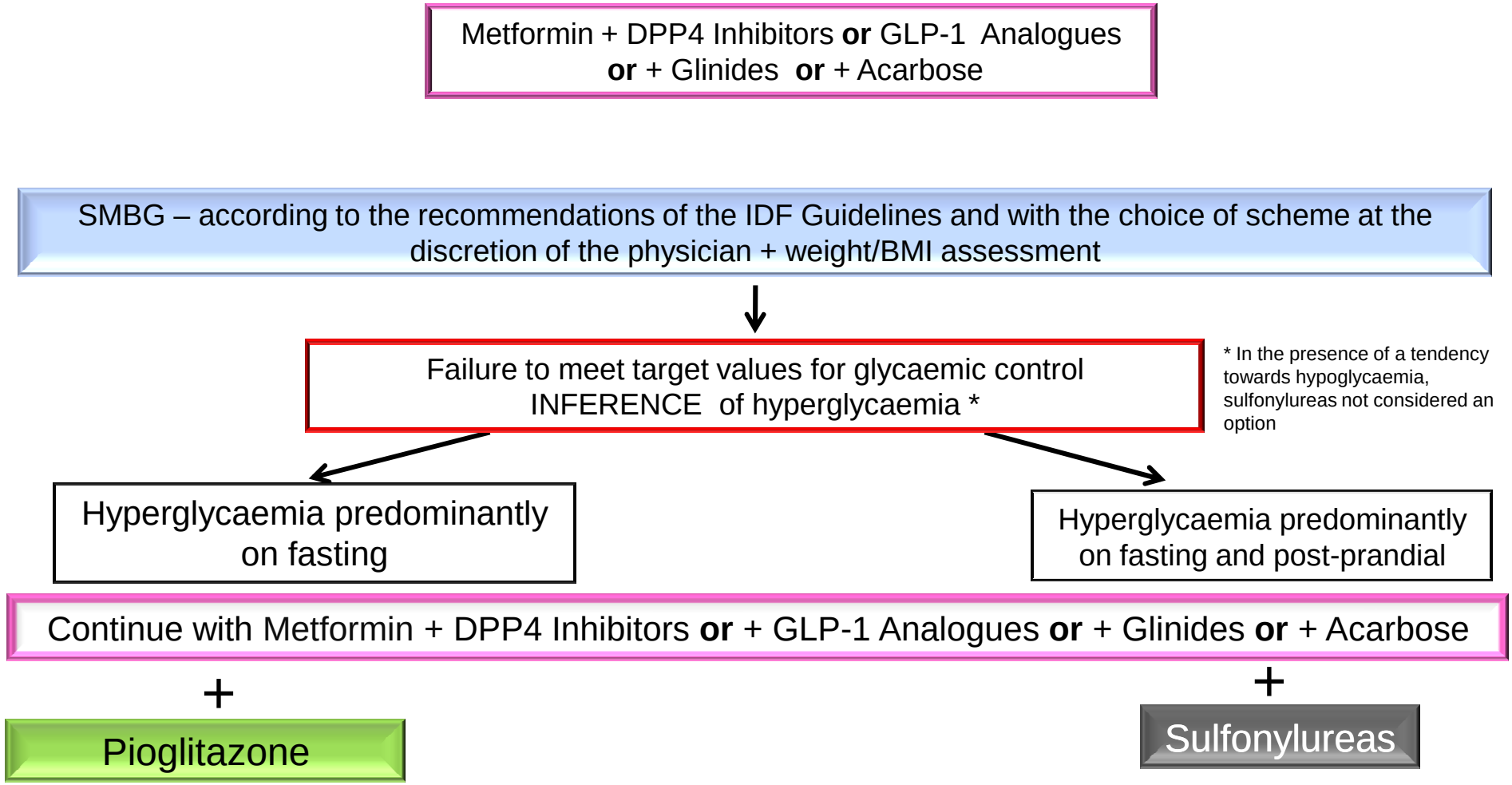
Algorithm B: Flowchart B2



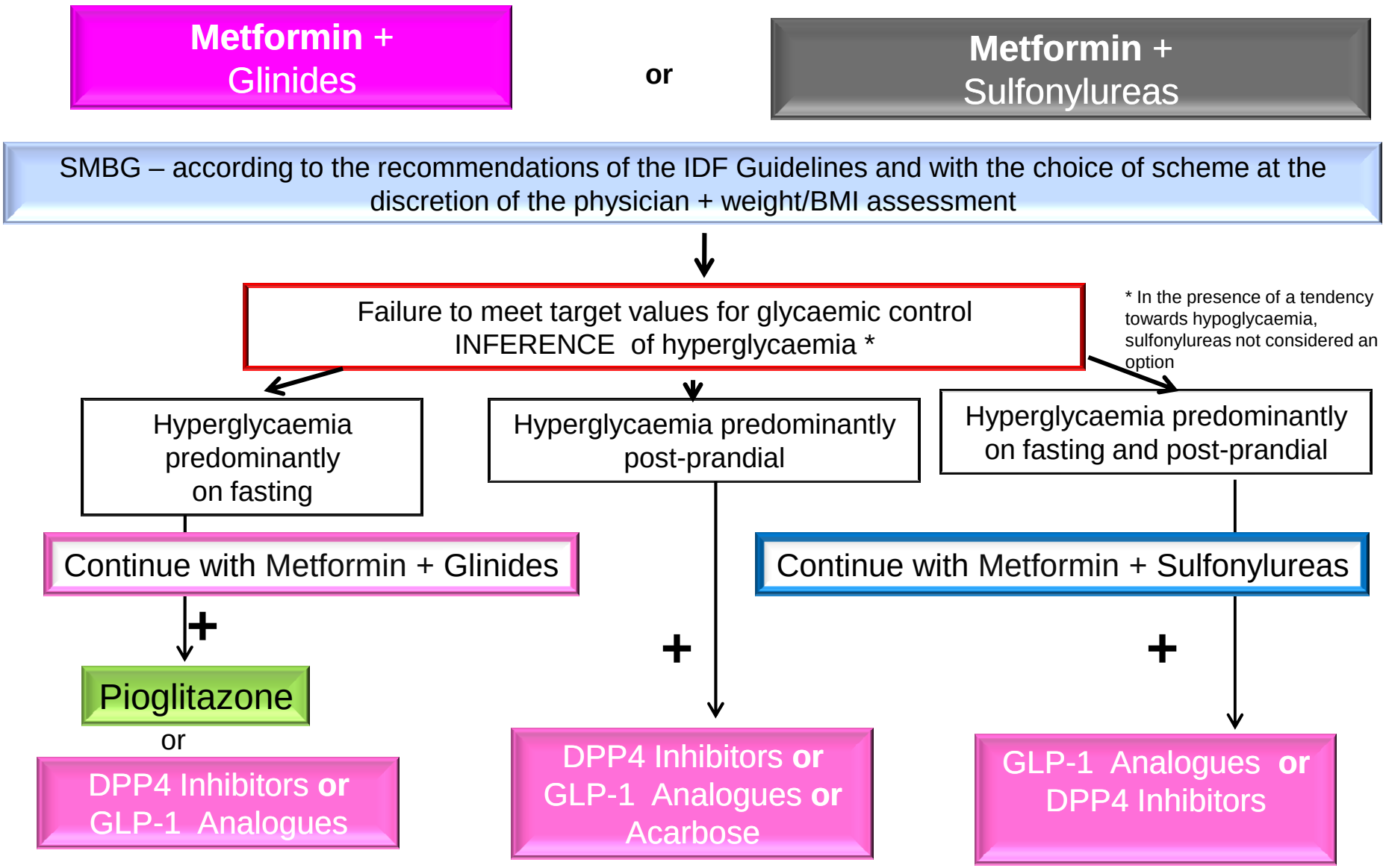
Algorithm B: Flowchart B3a



Algorithm B: Flowchart B3b



Algorithm B: Flowchart B3c



PERSONALIZING TREATMENT IN TYPE 2 DIABETES: AN INNOVATIVE APPROACH

AUTHORS
Antonio Ceriello, Vincenzo Armentano, Alberto De Micheli, Marco Gallo, Gabriele Perriello, Sandro Gentile.

On behalf of Associazione Medici Diabetologi (AMD)

www.aemmedi.it

Progetto SUBITO!AMD
Il grande progetto SUBITO! della diabetologia italiana (2009-2013)

Partecipa al Programma FAD **SUBITO!AMD**

Personalizza.SUBITO! (algoritmi terapeutici personalizzati)

IDF Algorithm for Personalized Treatment in Type 2 Diabetes
Members of the Development Group

Antonio Ceriello, Chair, Barcelona, Spain
Stephen Colagiuri, Chair, Sydney, Australia
Silver Bahendeka, Kampala, Uganda
Maha Barakat, Abudabi, United Arab Emirates
Xavier Cos, Barcelona, Spain
Alberto De Micheli, Genoa, Italy
Vivian Fonseca, Tulane, USA
Edwin Gale, Bristol, UK
Marco Gallo, Turin, Italy
Jorge Luiz Gross, San Paolo, Brasil
Stuart Harris, Toronto, Canada
Bernard Richterb. Dusseldorf, Germany
Wayne Sheu, Taipei, Taiwan
Eugene Sobngwi, London, UK
Johan Wens, Brussels, Belgium

International Diabetes Federation

Atypical Guidelines for individualising T2D treatment

- Newly-diagnosed - History of DT2 – Previous glycemic control, phenotype & background ?
- What is our A_{1c} target ?
- Look first to the control of other CVD risk factors
- How fast : rapidly, gradual…?
  - Evaluate patient's risk and vulnerability

Atypical Guidelines for individualising T2D treatment

- Newly-diagnosed - History of DT2 – Previous glycemic control, phenotype & background ?
- What is our A_{1c} target ?
- Look first to the control of other CVD risk factors
- How fast : rapidly, gradual…?
  - Evaluate patient's risk and vulnerability
- Select the best treatment for each patient:
  - Promote LSC and Diabetes Education:
    - Implement structured educational programs to motivate individuals with type 2 diabetes to assume a more active role in managing their condition
  - Drugs. Combine if necessary

Atypical Guidelines for individualising T2D treatment

- Newly-diagnosed - History of DT2 – Previous glycemic control, phenotype & background ?
- What is our A_{1c} target ?
- Look first to the control of other CVD risk factors
- How fast : rapidly, gradual…?
  - Evaluate patient's risk and vulnerability
- Select the best treatment for each patient:
  - Promote LSC and Diabetes Education:
  - Drugs. Combine if necessary
  - Reevaluate when necessary, including adherence

Challenges in increasing adherence

Reevaluate

Patient adherence to therapy

62% took tablets correctly in relation to food

20% regularly forgot to take their tablets

5% omitted tablets if their blood glucose was too high

2% omitted tablets if their blood glucose was too low

Browne DL, *et al. Diabet Med* 2000; **17:**528–531.

Atypical Guidelines for individualising T2D treatment. The ideal Diabetes Therapy

- Patients' perspective
  - Effective: underlying cause, robust sugar control, benefits beyond sugar control…
  - Easy of use: few steps, easy to learn, oral, any time of the day, o.i.d
  - Safe and tolerable
  - Inexpensive and reimbursable
- Physicians and health care professionals' perspective
  - Improves patients' health and outcomes: Efficacy to get targets, robust and durable control, safe, …
  - Easy to prescribe : no titration, no contraindications, no reimbursement pre-approval…
- Payors' perspective
  - Best outcomes at the lowest cost
  - Novel and added benefit (no place for a "me-too" drug")
  - Decrease short and long term treatment costs
  - Cost-effective

Diabetes Treatment Options: One Size Does NOT Fit All

Davida F. Kruger, MSN, APN-BC, BC-ADM, Editor-in-Chief

Clinical Diabetes
A PUBLICATION OF THE AMERICAN DIABETES ASSOCIATION®, INC.™

GRACIAS

THANK YOU

GRAZIE