3° Congresso congiunto SID AMD Sicilia.
Palermo 29-30 novembre 2018

Terapia di precisione o personalizzata nel diabete tipo 2: mito o realtà

Francesco Purrello
Direttore Dipt. di Medicina Clinica e Sperimentale
Direttore UOC Medicina, Ospedale Garibaldi
Presidente della Società Italiana di Diabetologia

Il Prof. Purrello dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

Novo, Lilly, Sanofi, MSD, Astra Zeneca, Boehringer, GSK

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

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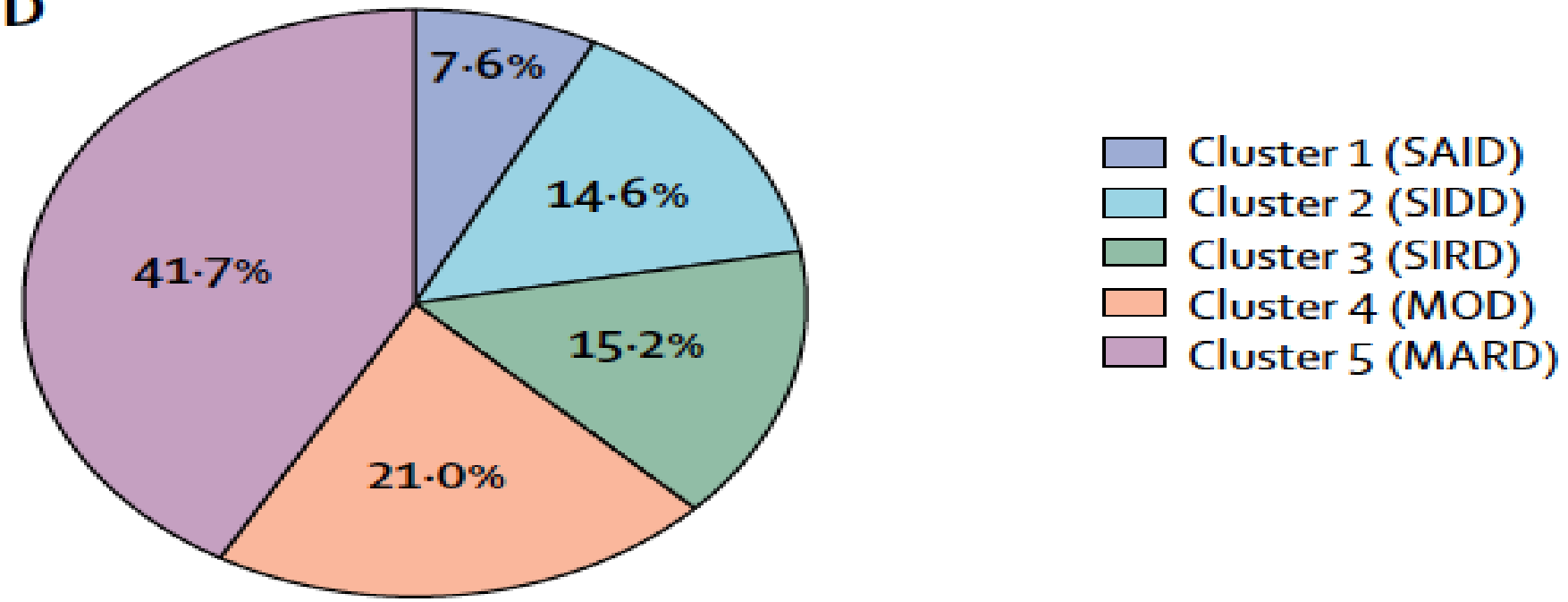
Terapia di precisione o personalizzata nel diabete tipo 2: mito o realtà

1. **Eterogeneità del fenotipo alla diagnosi**
2. **La medicina di precisione del DMT2**
3. **La medicina personalizzata del DMT2**

Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables

Lancet Diabetes Endocrinol 2018

D



SAID = severe autoimmune diabetes.
SIDD = severe insulin-deficient diabetes. **retinopatia**
SIRD = severe insulin-resistant diabetes. **nefropatia**
MOD = mild obesity-related diabetes.
MARD = mild age-related diabetes.

Precision medicine in diabetes: an opportunity for clinical translation

Jordi Merino [1,2] and Jose C. Florez[1,2,3]

Ann. N.Y. Acad. Sci. 1411 (2018) 140–152 © 2018

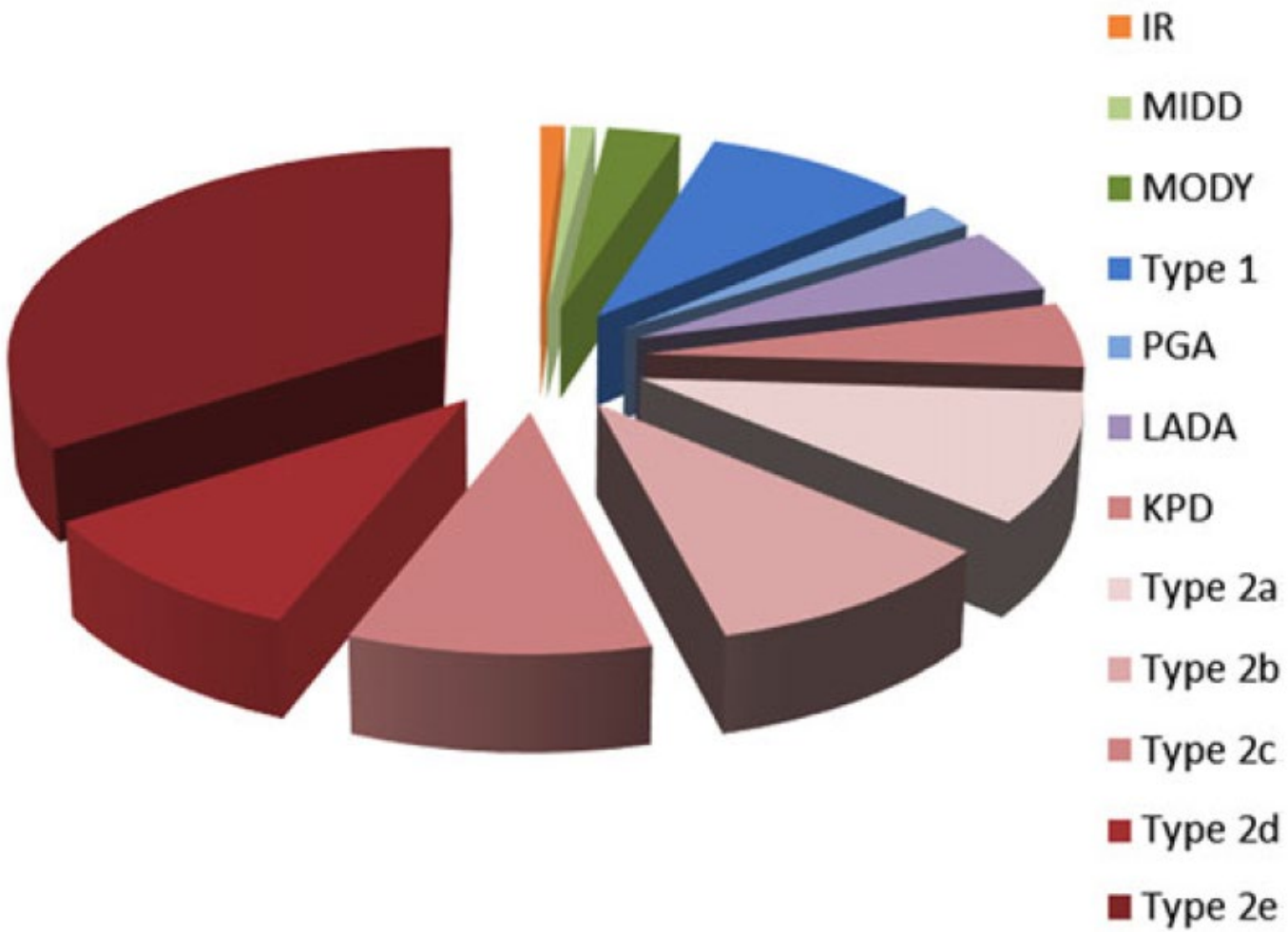
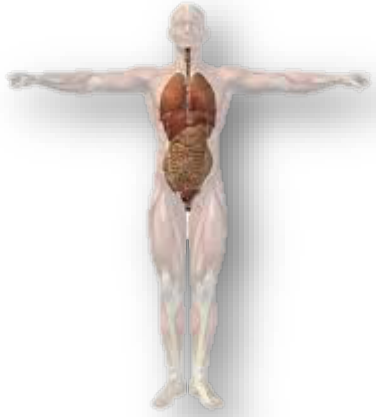


Figure 1. Heterogeneity of diabetes. The pie chart represents the multiple ways people can develop hyperglycemia and reach the diagnosis of diabetes. The size of each piece only represents an approximate proportion of prevalence in the population. IR, rare genetic forms of insulin resistance; MIDD, maternally inherited diabetes and deafness; MODY, maturity-onset diabetes of the young; type 1, type 1 diabetes; PGA, diabetes caused in the setting of polyglandular autoimmune syndrome; LADA, latent autoimmune diabetes of adults; KPD, ketosis-prone diabetes; type 2a–2e, hypothetical subgroups of type 2 diabetes.

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Diabete monogenico

MODY



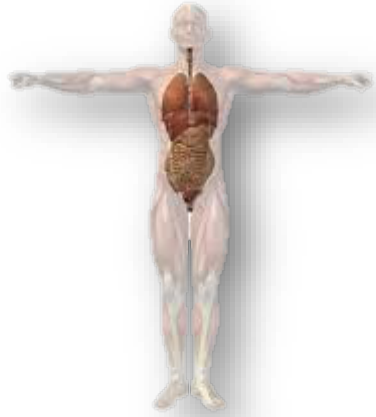
1 gene

HNF1A



1 terapia

Terapia di precisione



Diabete poligenico



multipli geni



multiple terapie

Table 1 | Summary of genetic mutations associated with maturity-onset diabetes of the young

Subtype	Gene	Location	Etiology	Features
MODY 1(82)	*HNF4α*	20q13.12	Insulin secretion defect	Progressive hyperglycemia
MODY 2(75)	Glucokinase	7p13	Glucose sensing and insulin secretion defect	Early onset; mild hyperglycemia, minor microvascular disease
MODY 3(83)	*HNF1α*	12q24.31	Insulin secretion defect	Progressive hyperglycemia, sensitive to SU
MODY 4(84)	*PDX1/IPF1*	13q12.2	Insulin secretion defect	Early onset
MODY 5(85)	*HNF1β*	17q12	Insulin secretion defect	Variable age at onset, range infancy to adult; progressive hyperglycemia, renal cysts; renal failure, require insulin treatment
MODY 6(86)	*NeuroD1*	2q31.3	Insulin secretion defect	Early onset
MODY 7(87)	*KLF11*	2p25.1	Insulin secretion defect	Very rare
MODY 8(88)	*CEL*	9q34.13	β-cell defect	Endocrine and exocrine pancreatic insufficiency
MODY 9(89)	*PAX4*	7q32.1	Little data	Very rare
MODY 10(90)	*INS*	11p15.5	Insulin secretion defect	Diagnosed in patients aged in their 20s to 30s. Can cause neonatal diabetes, antibody negative type 1 diabetes, and MODY
MODY 11(91)	*BLK*	8p23.1	Defect in insulin synthesis and secretion	Onset often before age 25 years; some patients require insulin for treatment
MODY 12(92)	*ABCC8*	11p15.1	Little data	Frequent cause of neonatal diabetes, but can rarely cause MODY
MODY 13(93)	*KCNJ11*	11p15.1	Insulin secretion defect	Sulfonylurea therapy effective
MODY 14(94)	*APPL1*	3p14.3	Defect in insulin signaling pathway	With elevated FBG and HbA1C and onset between 30s and 50s

Review

Precision medicine in the management of type 2 diabetes

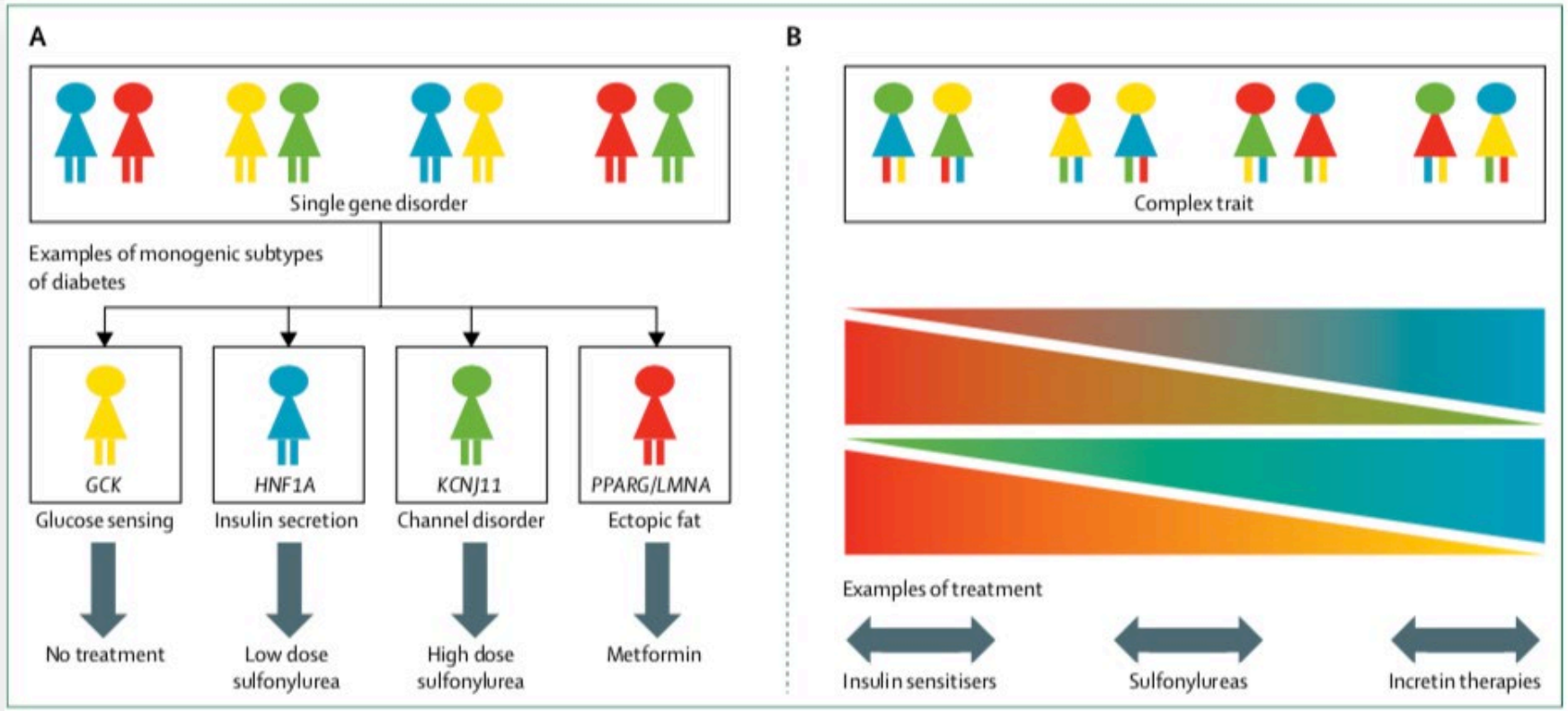
Anna L Gloyn, Daniel J Drucker

The study of type 2 diabetes has been driven by advances in human genetics, epigenetics, biomarkers, mechanistic studies, and large clinical trials, enabling new insights into disease susceptibility, pathophysiology, progression, and development of complications. Simultaneously, several new drug classes with different mechanisms of action have been introduced over the past two decades, accompanied by data about cardiovascular safety and non-glycaemic outcomes. In this Review, we critically examine the progress and integration of this new science into clinical practice, and review opportunities for enabling the use of precision medicine in the diagnosis and treatment of type 2 diabetes. We contrast the success in delivering personalised medicine for monogenic diabetes with the greater challenge of providing a precision medicine approach for type 2 diabetes, highlighting gaps, limitations, and areas requiring further study.

Lancet Diabetes Endocrinol 2018

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April 23, 2018
http://dx.doi.org/10.1016/S2213-8587(18)30052-4

Oxford Centre for Diabetes, Endocrinology and Metabolism, Radcliffe Department of Medicine, and Wellcome Centre for Human Genetics, University of Oxford,

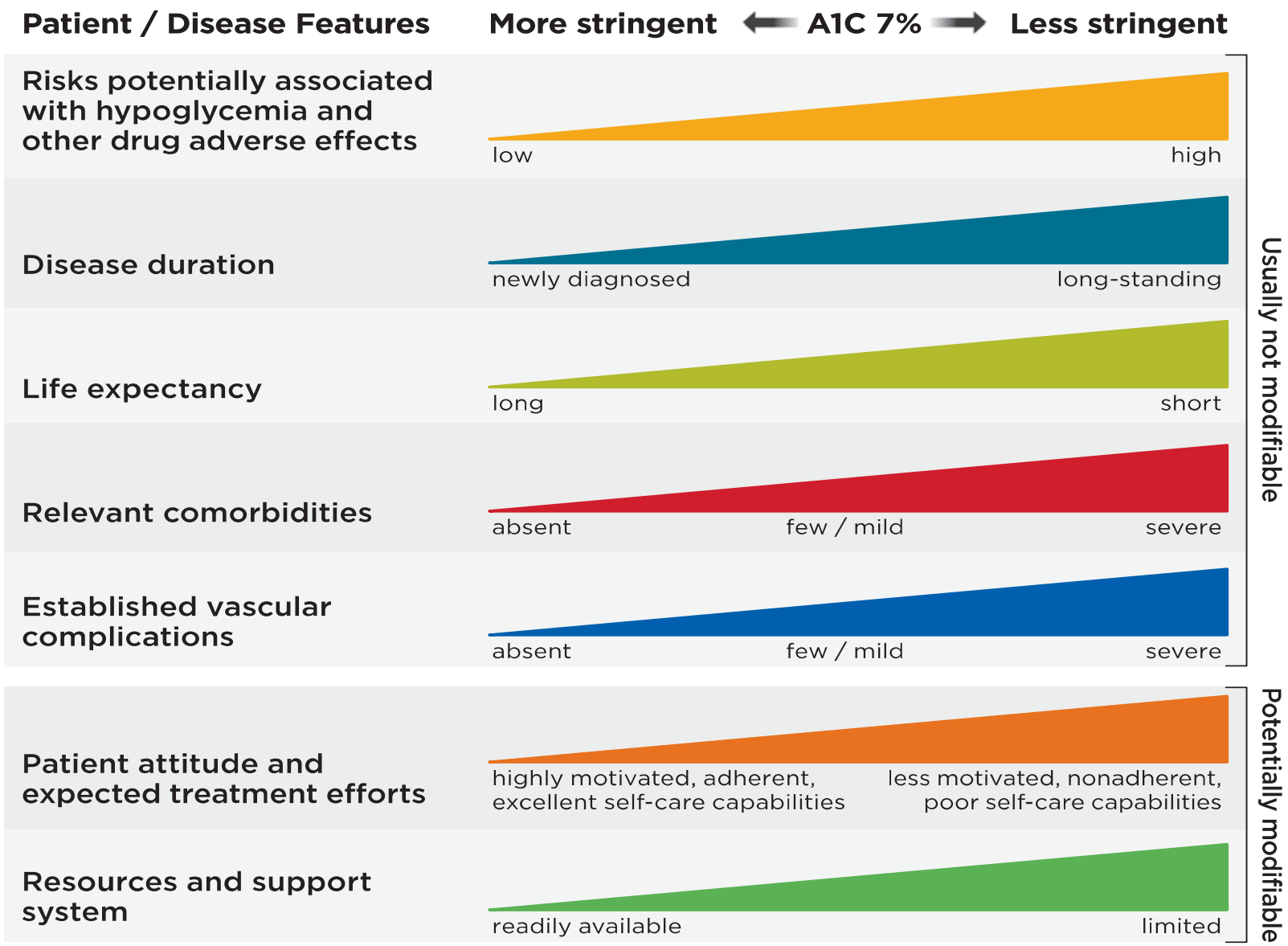


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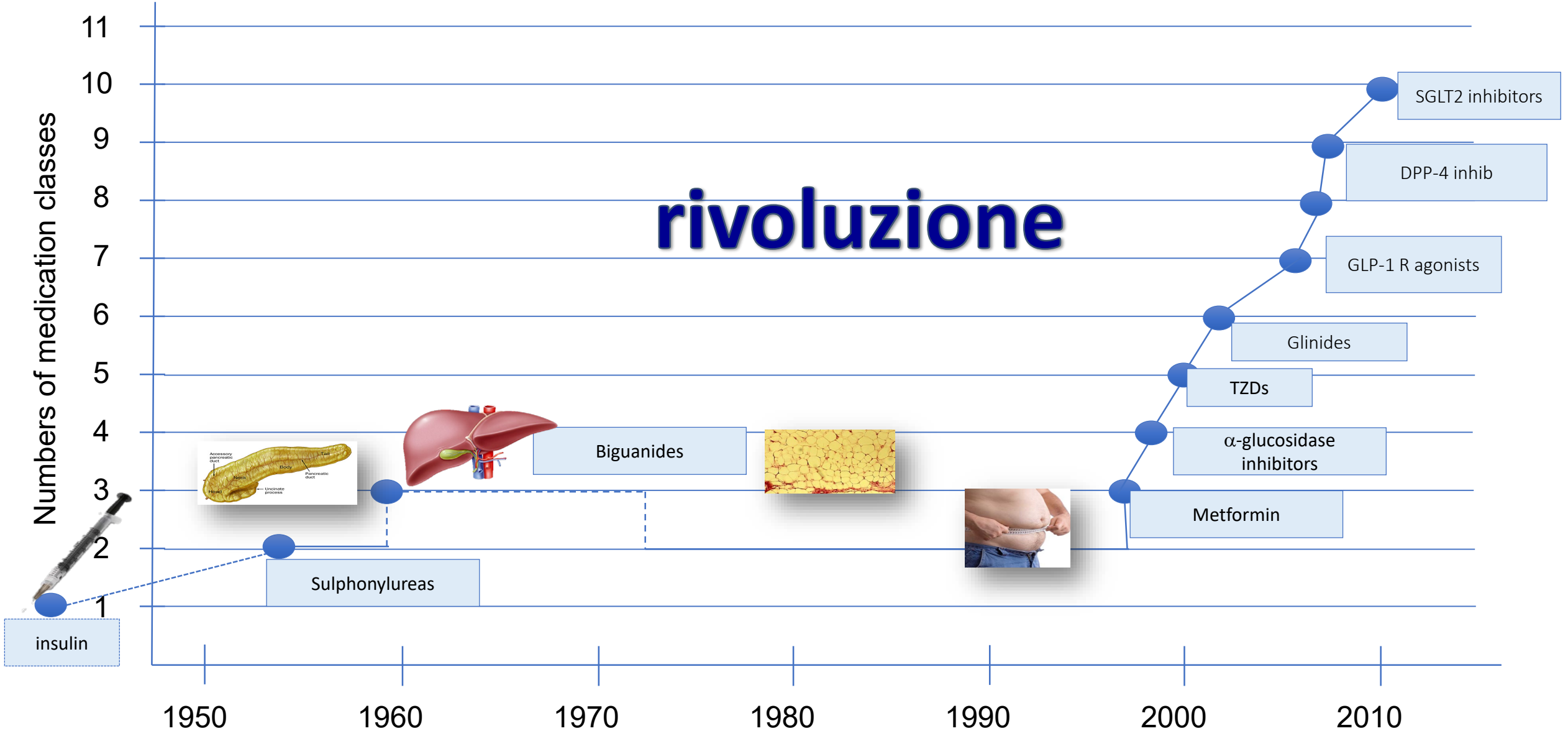
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3. **La medicina personalizzata del DMT2**

Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach.



Evoluzione della terapia del diabete tipo 2



Steven E. Kahn, M.B., Ch.B., Mark E. Cooper, M.B., B.S, Ph.D., and Stefano Del Prato, M.D. (2014).
PATHOPHYSIOLOGY AND TREATMENT OF TYPE 2 DIABETES: PERSPECTIVES ON THE PAST, PRESENT AND FUTURE.
Lancet, *383*(9922), 1068–1083. http://doi.org/10.1016/S0140-6736(13)62154-6

Terapia di precisione o personalizzata nel diabete tipo 2: mito o realtà

Terapia “personalizzata”

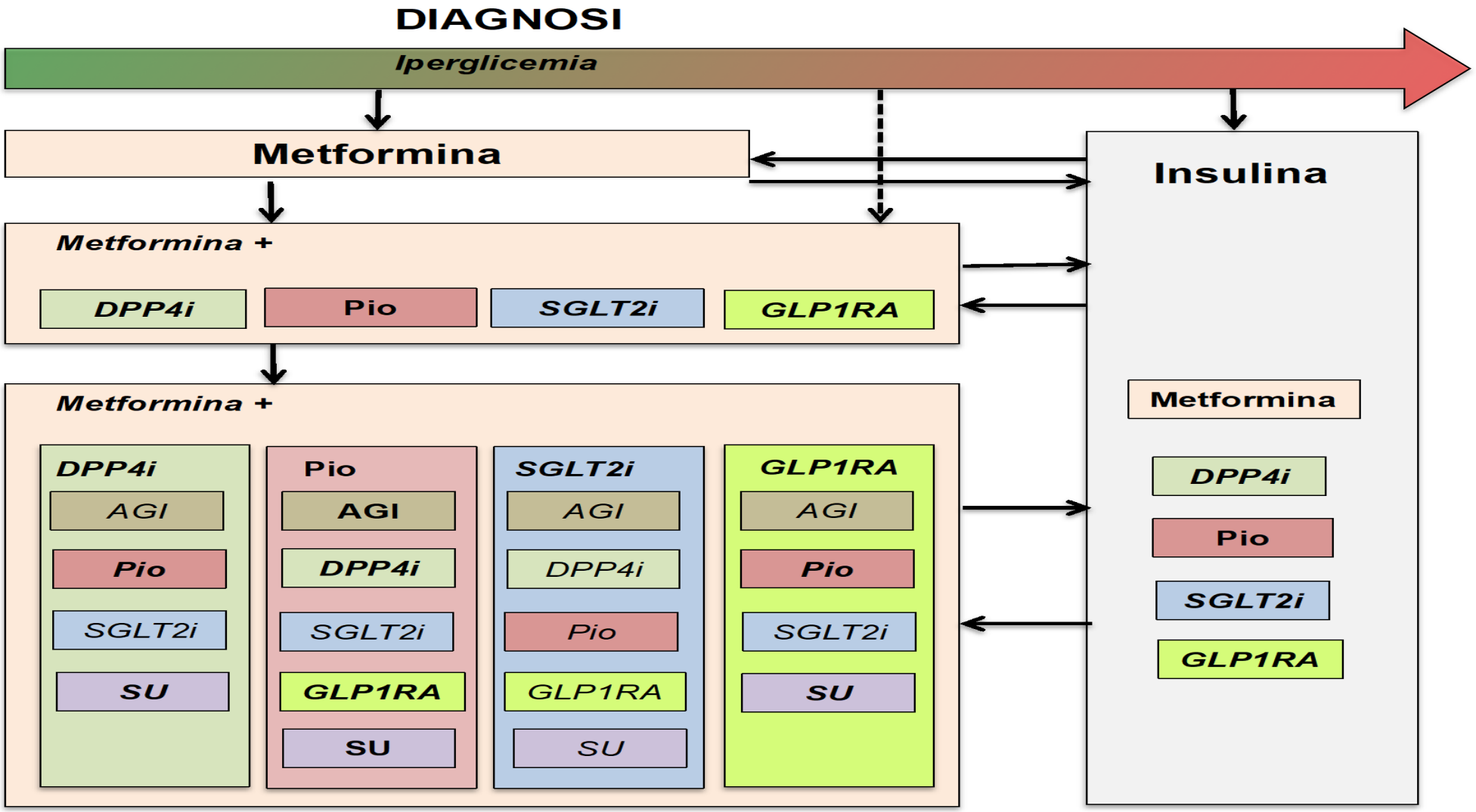
- in base alle complicanze cardiovascolari o renali

- in base all’età e al rischio di ipoglicemia

- in base al peso corporeo

STANDARD 2018

L'algoritmo della terapia farmacologica del diabete di tipo 2



GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH

FIRST-LINE THERAPY IS METFORMIN AND COMPREHENSIVE LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY)
IF HbA_{1c} ABOVE TARGET PROCEED AS BELOW

TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

ESTABLISHED ASCVD OR CKD

NO

WITHOUT ESTABLISHED ASCVD OR CKD

ASCVD PREDOMINATES

EITHER/OR

- GLP-1 RA with proven CVD benefit[1]
- SGLT2i with proven CVD benefit[1], if eGFR adequate[2]

If HbA_{1c} above target

If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:

- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
- DPP-4i if not on GLP-1 RA
- Basal insulin[4]
- TZD[5]
- SU[6]

HF OR CKD PREDOMINATES

PREFERABLY
SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[2]

OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1 RA with proven CVD benefit[1]

If HbA_{1c} above target

- Avoid TZD in the setting of HF

Choose agents demonstrating CV safety:

- Consider adding the other class with proven CVD benefit[1]
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal insulin[4]
- SU[6]

COMPELLING NEED TO MINIMISE HYPOGLYCAEMIA

DPP-4i	GLP-1 RA	SGLT2i[2]	TZD
If HbA_{1c} above target			
SGLT2i[2] **OR** TZD	SGLT2i[2] **OR** TZD	GLP-1 RA **OR** DPP-4i **OR** TZD	SGLT2i[2] **OR** DPP-4i **OR** GLP-1 RA

If HbA_{1c} above target

Continue with addition of other agents as outlined above

If HbA_{1c} above target

Consider the addition of SU[6] **OR** basal insulin:

- Choose later generation SU with lower risk of hypoglycaemia
- Consider basal insulin with lower risk of hypoglycaemia[7]

COMPELLING NEED TO MINIMISE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

EITHER/OR

- GLP-1 RA with good efficacy for weight loss[8]
- SGLT2i[2]

If HbA_{1c} above target

SGLT2i[2]	GLP-1 RA with good efficacy for weight loss[8]
If HbA_{1c} above target	

If triple therapy required or SGLT2i and/or GLP-1 RA not tolerated or contraindicated use regimen with lowest risk of weight gain

PREFERABLY

DPP-4i (if not on GLP-1 RA) based on weight neutrality

If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:

COST IS A MAJOR ISSUE[9–10]

SU[6]	TZD[10]
If HbA_{1c} above target	
TZD[10]	SU[6]
If HbA_{1c} above target	

- **Insulin therapy** basal insulin with lowest acquisition cost

OR

- Consider DPP-4i **OR** SGLT2i with lowest acquisition cost[10]

1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycaemia
7. Degludec / glargine U300 > glargine U100 / detemir > NPH insulin

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH

ESTABLISHED ASCVD OR CKD

UDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY)
D AS BELOW

TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

ASCVD PREDOMINATES

EITHER/ OR

GLP-1 RA with proven CVD benefit[1]

SGLT2i with proven CVD benefit[1], if eGFR adequate[2]

If HbA_{1c} above target

If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:

- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
- DPP-4i if not on GLP-1 RA
- Basal insulin[4]
- TZD[5]

HF OR CKD PREDOMINATES

PREFERABLY
SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3]

OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1 RA with proven CVD benefit[1]

If HbA_{1c} above target

- Avoid TZD in the setting of HF

Choose agents demonstrating CV safety:

- Consider adding the other class with proven CVD benefit[1]
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal insulin[4]
- SU[6]

WITHOUT ESTABLISHED ASCVD OR CKD

CAEMIA

TZD

If HbA_{1c} above target

SGLT2i[2] OR DPP-4i OR GLP-1 RA

d above

ects

COMPELLING NEED TO MINIMISE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

EITHER/ OR

GLP-1 RA with good efficacy for weight loss[8]

SGLT2i[2]

If HbA_{1c} above target

SGLT2i[2]

GLP-1 RA with good efficacy for weight loss[8]

If HbA_{1c} above target

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PREFERABLY

DPP-4i (if not on GLP-1 RA) based on weight neutrality

If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:

COST IS A MAJOR ISSUE[9-10]

SU[6]

TZD[10]

If HbA_{1c} above target

TZD[10]

SU[6]

If HbA_{1c} above target

- Insulin therapy basal insulin with lowest acquisition cost

OR

- Consider DPP-4i **OR** SGLT2i with lowest acquisition cost[10]

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH

FIRST-LINE THERAPY IS METFORMIN AND COMPREHENSIVE LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY)
IF HbA_{1c} ABOVE TARGET PROCEED AS BELOW

TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

ESTABLISHED ASCVD OR CKD

ASCVD PREDOMINATES

EITHER/OR

- GLP-1 RA with proven CVD benefit[1]
- SGLT2i with proven CVD benefit[1], if eGFR adequate[2]

If HbA_{1c} above target

If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:

- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
- DPP-4i if not on GLP-1 RA
- Basal insulin[4]
- TZD[5]
- SU[6]

HF OR CKD PREDOMINATES

PREFERABLY
SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[2]

OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1 RA with proven CVD benefit[1]

If HbA_{1c} above target

- Avoid TZD in the setting of HF

Choose agents demonstrating CV safe

- Consider adding the other class with proven CVD benefit[1]
- DPP-4i (not saxagliptin) in the set of HF (if not on GLP-1 RA)
- Basal insulin[4]
- SU[6]

COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA

DPP-4i	GLP-1 RA	SGLT2i[2]	TZD
If HbA_{1c} above target	If HbA_{1c} above target	If HbA_{1c} above target	If HbA_{1c} above target
SGLT2i[2] **OR** TZD	SGLT2i[2] **OR** TZD	GLP-1 RA **OR** DPP-4i **OR** TZD	SGLT2i[2] **OR** DPP-4i **OR** GLP-1 RA

If HbA_{1c} above target

Continue with addition of other agents as outlined above

If HbA_{1c} above target

WEIGHT LOSS

COST IS A MAJOR ISSUE[9–10]

- SU[6]
- TZD[10]

If HbA_{1c} above target

- TZD[10]
- SU[6]

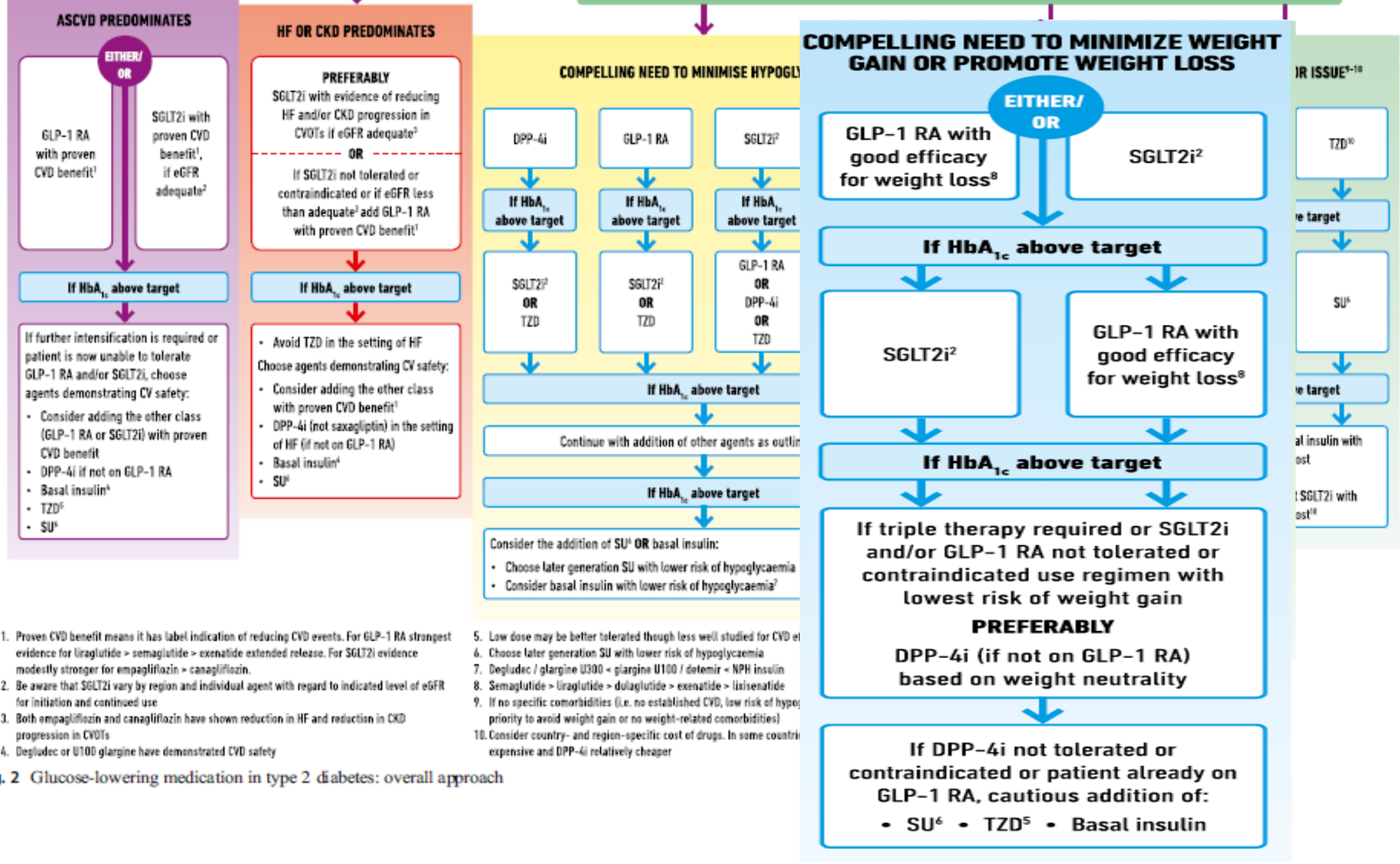
If HbA_{1c} above target

- Insulin therapy basal insulin with lowest acquisition cost

OR

- Consider DPP-4i **OR** SGLT2i with lowest acquisition cost[10]

1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strong evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD e
6. Choose later generation SU with lower risk of hypoglycaemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypo priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countri expensive and DPP-4i relatively cheaper

Fig. 2 Glucose-lowering medication in type 2 diabetes: overall approach

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH

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IF HbA_{1c} ABOVE TARGET PROCEED AS BELOW

ESTABLISHED ASCVD OR CKD

NO

WITHOUT ESTABLISHED AS

ASCVD PREDOMINATES

EITHER/ OR

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- SGLT2i with proven CVD benefit[1], if eGFR adequate[2]

If HbA_{1c} above target

If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:

- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
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- Basal insulin[4]
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- SU[6]

HF OR CKD PREDOMINATES

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- Basal insulin[4]
- SU[6]

COMPELLING NEED TO MINIMISE HYPOGLYCAEMIA

DPP-4i	GLP-1 RA	SGLT2i[2]	TZD
If HbA_{1c} above target			
SGLT2i[2] **OR** TZD	SGLT2i[2] **OR** TZD	GLP-1 RA **OR** DPP-4i **OR** TZD	SGLT2i[2] **OR** DPP-4i **OR** GLP-1 RA

If HbA_{1c} above target

Continue with addition of other agents as outlined above

If HbA_{1c} above target

Consider the addition of SU[6] **OR** basal insulin:

- Choose later generation SU with lower risk of hypoglycaemia
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COMPELLIN… GAIN O…

GLP-1 RA good eff… for weigh…

SGLT…

If triple … and/or … contrai… low…

DPP… bas…

If … contrain… GLP-1…

COST IS A MAJOR ISSUE[9-10]

SU[6] | TZD[10]

If HbA_{1c} above target

TZD[10] | SU[6]

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Il Diabete ed il ruolo del Diabetologo: punti di vista

- Malattia spesso di facile inquadramento e di facile gestione
- Malattia che in molti casi non richiede la consulenza dello specialista
- Solo in caso di gravi complicanze (importante scompenso metabolico, piede diabetico ..) è necessario ricorrere al diabetologo

Malattia complessa, eterogenea nel fenotipo e nella patogenesi

Malattia che richiede fin dalla diagnosi la consulenza iniziale dello specialista

Il diabetologo deve essere periodicamente consultato, anche in pazienti con buon controllo metabolico, per ottimizzare la scelta dei farmaci ipoglicemizzanti e personalizzare la terapia

Il Diabete ed il ruolo del Diabetologo: punti di vista

- **Solo lo specialista diabetologo è in grado di conoscere ed utilizzare tutti gli strumenti terapeutici oggi a disposizione per individuare il farmaco corretto per il proprio paziente.**

- **Il mancato o scarso utilizzo di queste risorse e l'inerzia terapeutica rischiano di delegittimare ed indebolire la nostra figura professionale.**