

GRG-Journal Club
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I NUOVI FARMACI IPOGLICEMIZZANTI

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Diabete mellito

- **Alterazione del metabolismo**
- **Sindrome cardio-vascolare**

Caratterizzata principalmente da Iperglicemia cronica

Diagnosi di Diabete mellito

- **Glicemia a digiuno ripetuta > 126 mg/dl**
- **Glicemia dopo OGTT (75g) > 200mg/dl**
- **Sintomi e glicemia casuale > 200 mg/dl**
- **Emoglobina glicata > 48 mmol/mol**

Diabete mellito tipo 1: (distruzione delle cellule beta pancreatiche, deficit assoluto d'insulina)

- a) Immunomediato
- b) Idiopatico

Diabete mellito tipo 2: varia da una predominante insulino resistenza con relativa carenza di insulina ad un predominante difetto secretorio associato ad insulino-resistenza

Altri tipi specifici:

- a) difetti genetici della cellule beta pancreatiche (MODY 1-6, difetti cromosomici)
- b) difetti genetici nell'azione dell'insulina (es. diabete lipoatrofico)
- c) patologie del pancreas esocrino (es pancreatiti)
- d) malattie endocrine (es ipertiroidismo, S. di Cushing)
- e) da farmaci (es. glucocorticoidi)
- f) infezioni (es. citomegalovirus)
- g) rare forme immunomEDIATE (es. Ab anti recettore insulinico)
- h) altre sindromi genetiche che a volte si associano al diabete (es. S. Down, S. Turner)
- i) diabete gestazionale

Pre-Diabete

- **Iperglicemia a digiuno (IFG): 100 – 125 mg/dl**
- **Ridotta tolleranza glucidica (IGT): dopo curva da carico orale 140 – 199 mg/dl**
- **Emoglobina glicata (A1c) 42 - 48 mmol/mol**

Pre-Diabete, conseguenze

- **Sviluppo di Diabete mellito**
- **Coronarosclerosi**
- **Insufficienza cardiaca (Disfunzione diastolica)**

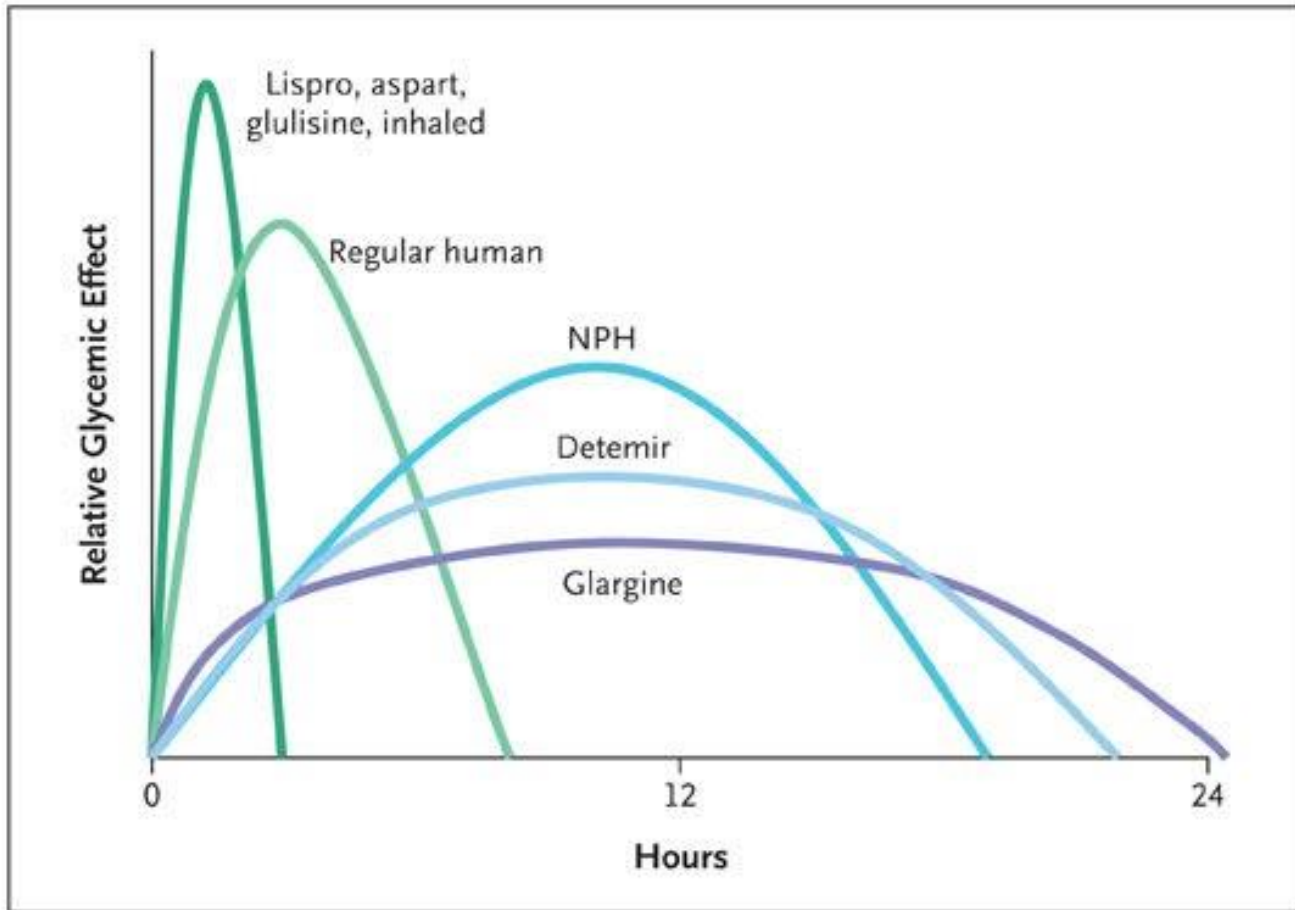
Nell'anziano (> 65anni)

- **Diabete mellito** **25%**
- **Pre-diabete** **50%**
- **Normale** **25%**

Diabete mellito tipo 1

- **Distruzione beta-cellulare**
 - **Meccanismo immunologico**
- **Deficienza insulinica assoluta**

CURVE TEMPO-ATTIVITA' DEGLI ANALOGHI INSULINICI







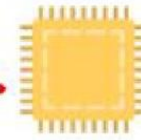


Technology availability

In a near future
Already used by
patients with diabetes



Smart contact lenses
(glucose level)



Flash or Continuous Glucose Monitor
(glucose level, hyper- & hypoglycemia, time in range...)



Smart Blood Pressure Monitor



Smart ECG
(arrhythmia)



Smart Watch
(activity, sleep, glucose level, heart rate, geolocation)



Smart Drugs
(drug regimen compliance, physiological response to treatment, body temperature...)



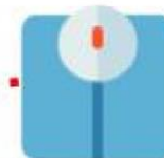
Apps
(control of connected devices, medical records, telemedicine, social media, online patients community)



Artificial Pancreas



Smart Socks
(temperature, inflammation, infection and amputation prevention)



Smart Weighing Scale
(weight, body mass index, %fat mass, pulse wave velocity)

Diabete mellito tipo 2

- **Alterazione della funzione insulinica**
 - **Resistenza insulinica**
- **Alterazione della funzione beta-cellulare**
 - **Difetto di secrezione insulinica**

Type 2 Diabetes Is NOT a Mild Disease

Diabetic retinopathy

Leading cause of blindness in working-age adults¹



Diabetic nephropathy

Leading cause of end-stage renal disease²



Stroke

2- to 4-fold increase in cardiovascular mortality and stroke³



Cardiovascular disease

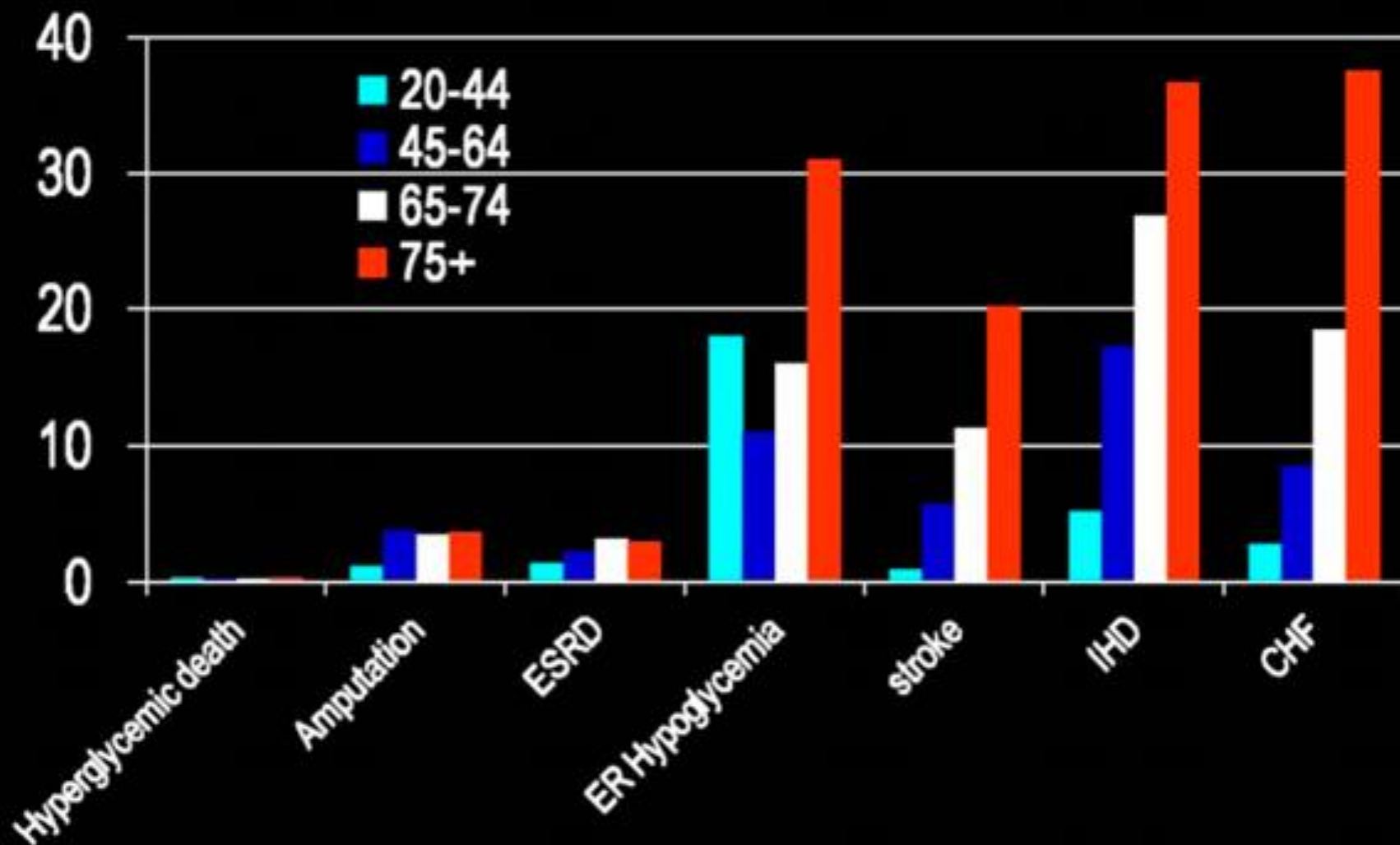
8/10 diabetic patients die from CV events⁴



Diabetic neuropathy

Leading cause of non-traumatic lower extremity amputations⁵

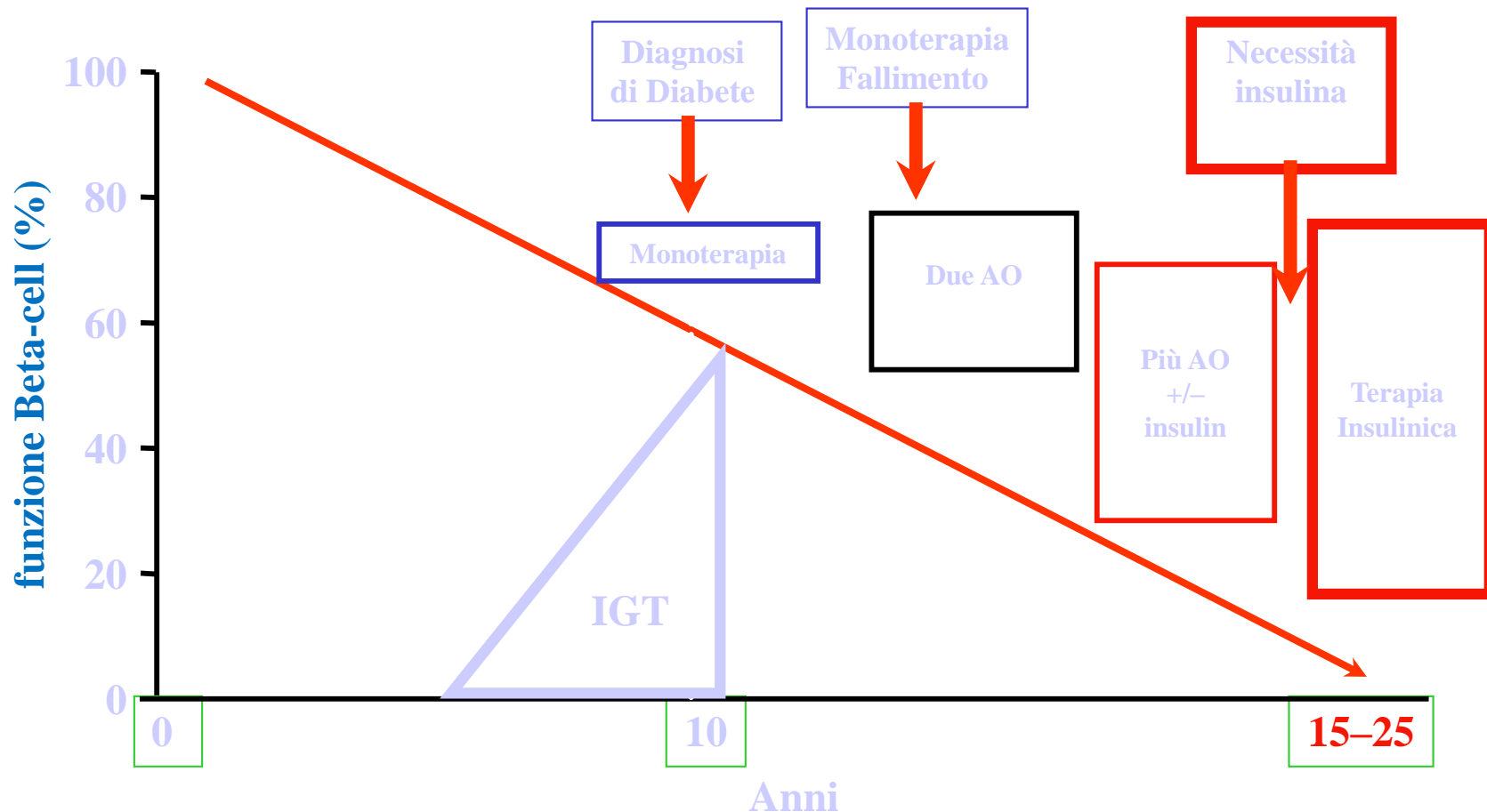
Incidence (per 1000) of Major Diabetes Complications According to Age among Adults with Diabetes, 2009



Si associa più frequentemente a:

- **Morte prematura**
- **Disabilità funzionale**
- **Sarcopenia accelerata**
- **Condizioni concomitanti**
 - **Ipertensione arteriosa**
 - **Cardiopatía ischemica**
 - **Ictus cerebrale**

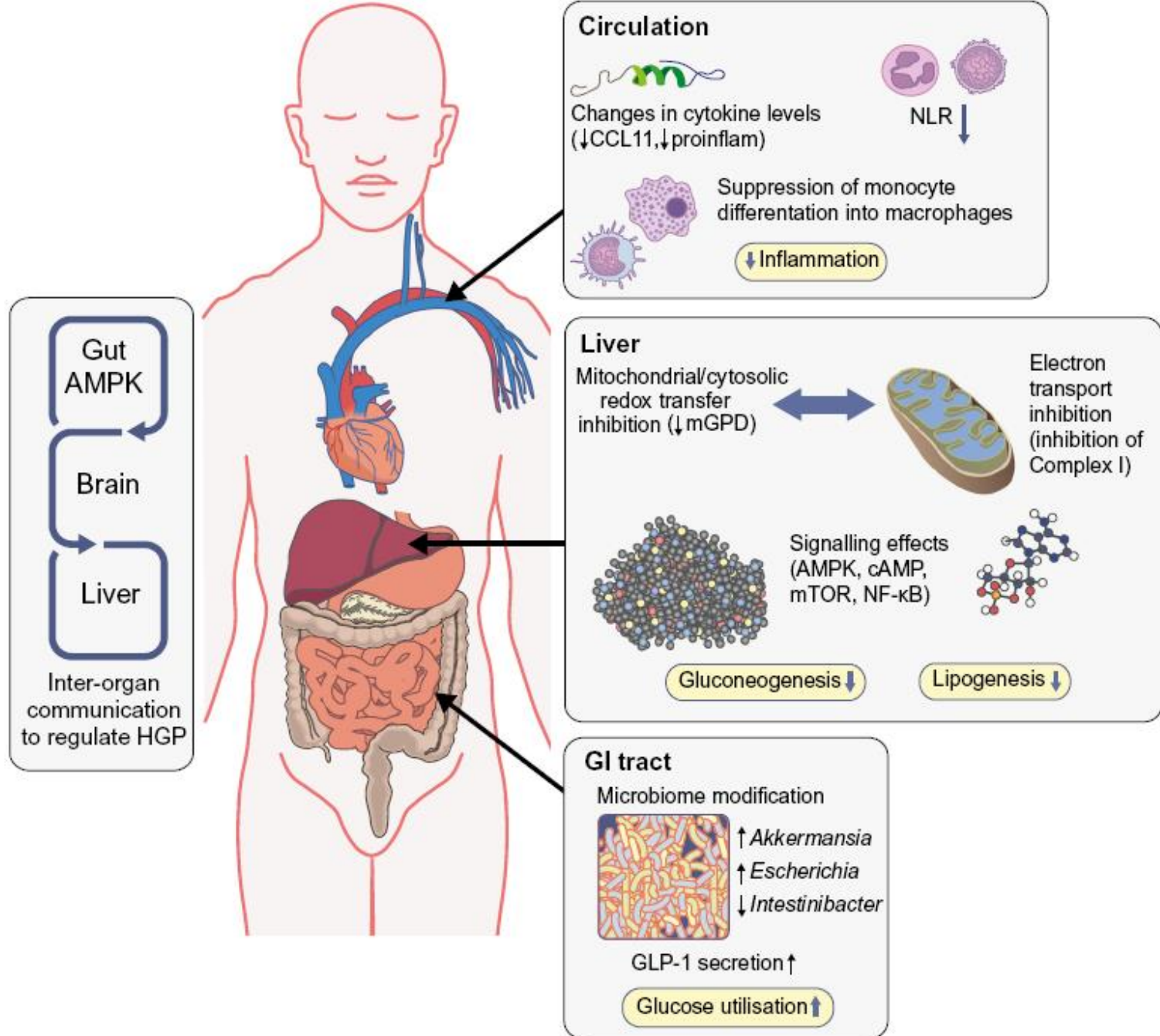
Progressivo incremento della terapia in funzione della durata del diabete



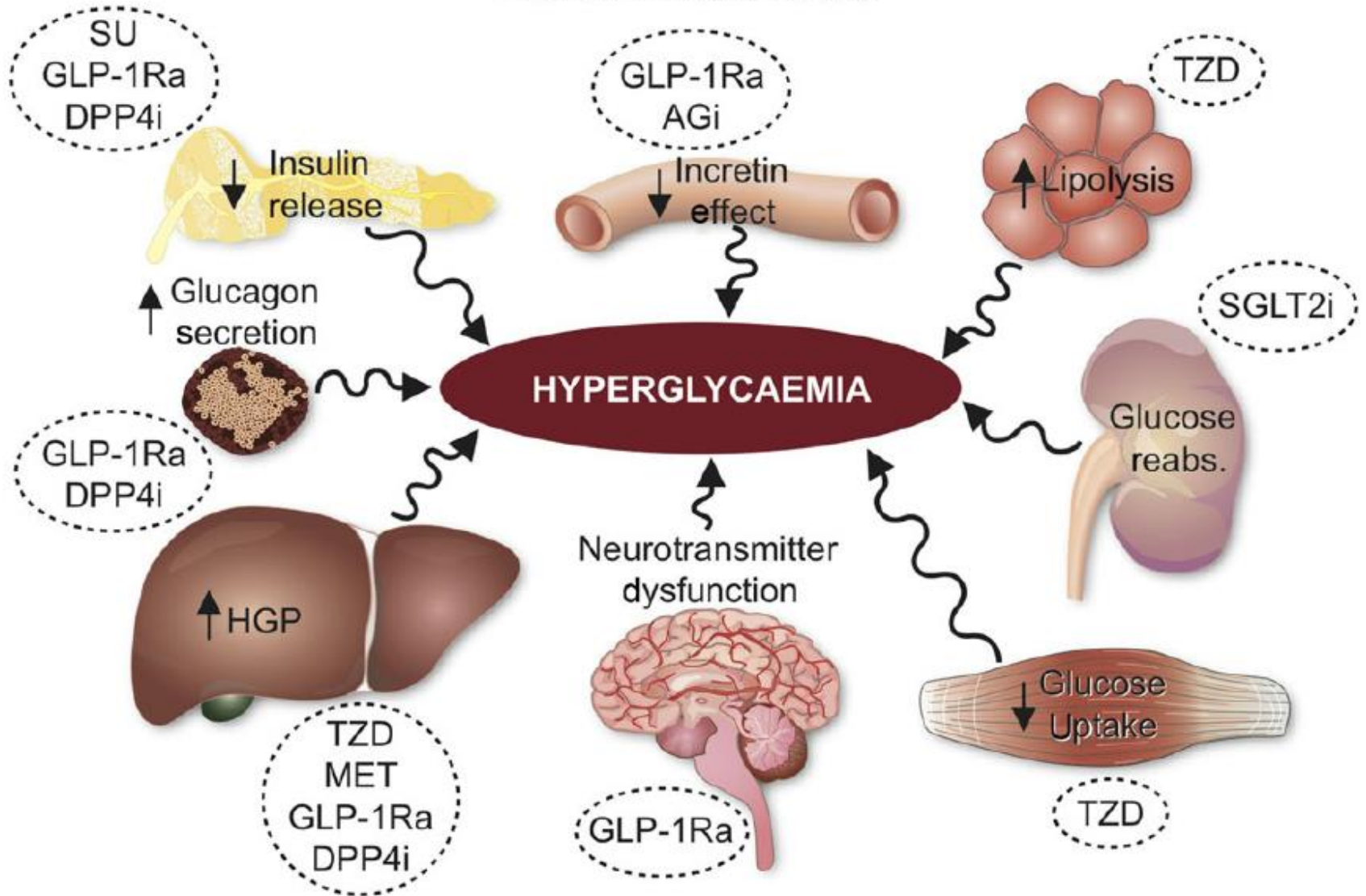
IGT=impaired glucose tolerance.

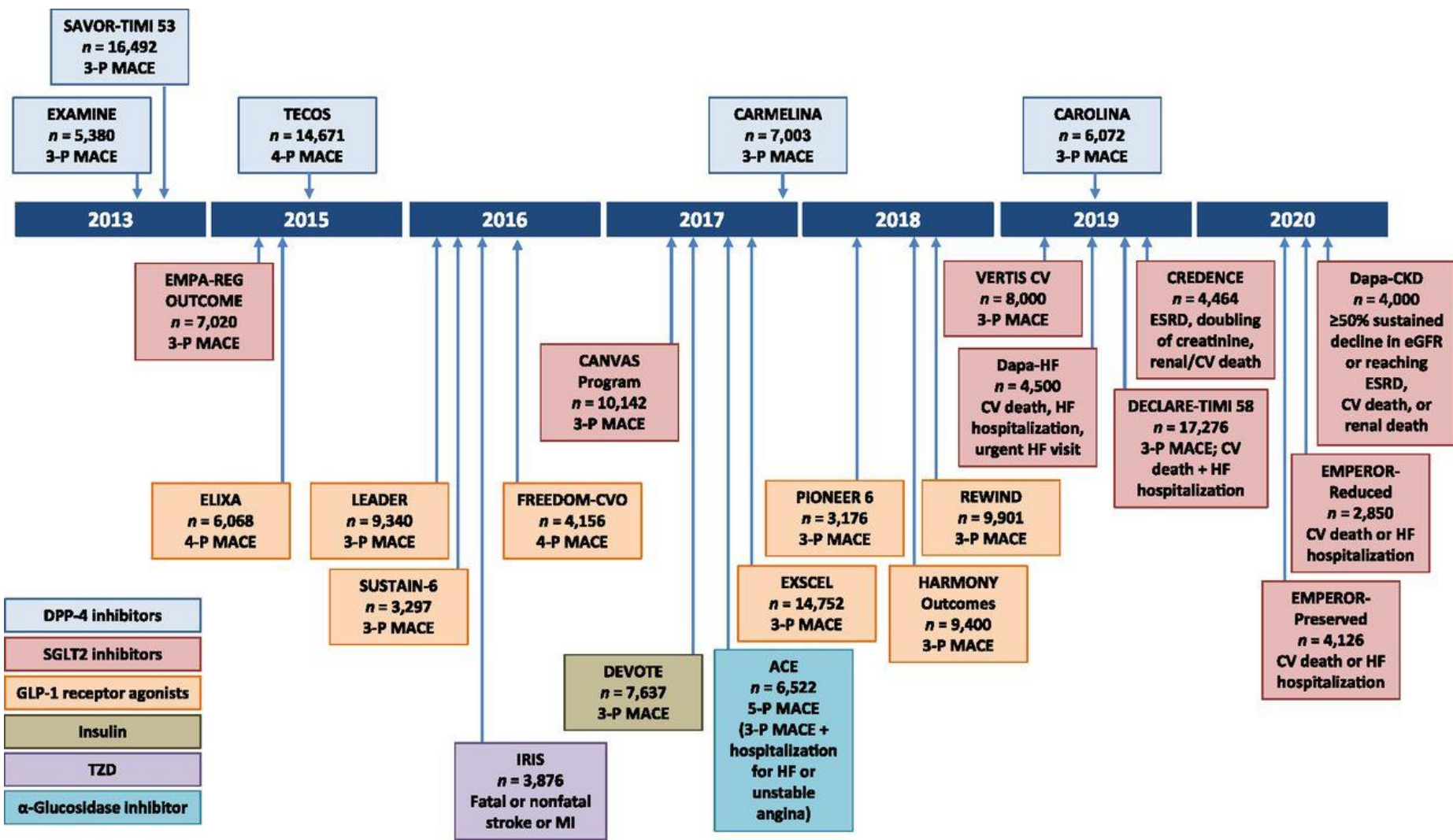
UKPDS 16. *Diabetes*. 1995;44:1249-1258.

Turner RC et al. *JAMA*. 1999;281:2005-2012; Warren RE. *Diabetes Res Clin Pract*. 2004;65:S3-S8; Lebovitz HE. *Med Clin N Am*. 2004;88:847-863.



The ominous octet

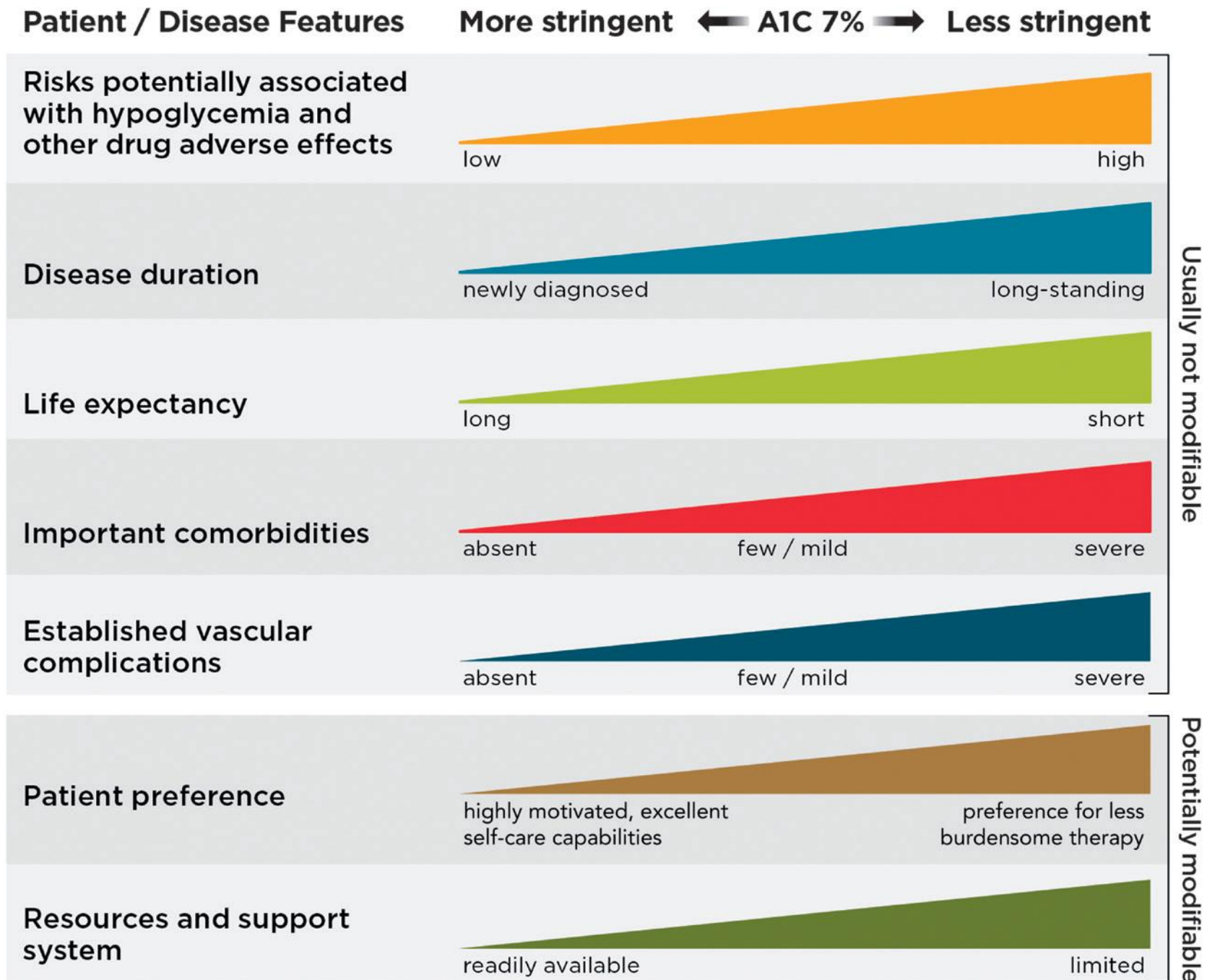




CATEGORIE DI PAZIENTI

- 1. Relativamente sani, indipendenti, aspettativa > 15a, senza comorbilità, complicanze minime, A1c <58, FPG 90-130, PA<140/90mmHg, statina**
- 2. Fragili, dipendenti, aspettativa 5- 15a, complessi, con malattie croniche coesistenti, complicanze moderate, A1c <64, FPG 90-150, PA<140/90mmHg, statina**
- 3. Terminali, molto anziani, aspettativa < 5a, molto complessi, malattie croniche avanzate, complicanze evolute, A1c <69, FPG 100-180, PA<150/90mmHg, statina da valutare**

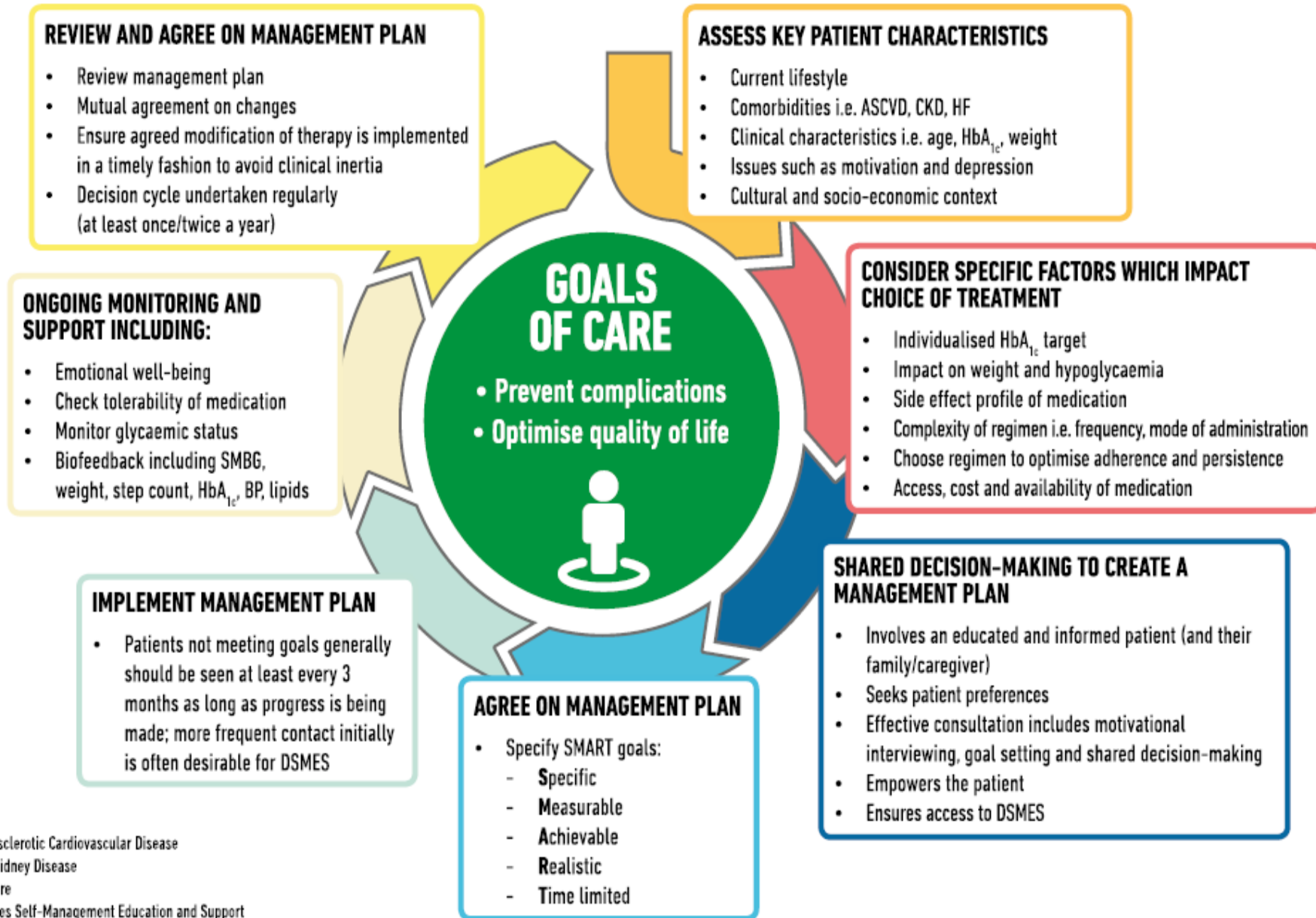
Approach to Individualization of Glycemic Targets



PARTNERSHIP MEDICO-PAZIENTE

- **Valutazione dei benefici di un controllo glicemico intensivo, considerata l'aspettativa di vita**
- **Valutazione dei possibili danni**
- **Stabilire un obiettivo glicemico individuale, che massimizzi i benefici e riduca la probabilità di danni, tenendo conto delle preferenze del paziente**
- **Minimizzare la complessità della terapia**

DECISION CYCLE FOR PATIENT-CENTRED GLYCAEMIC MANAGEMENT IN TYPE 2 DIABETES



ASCVD = Atherosclerotic Cardiovascular Disease
CKD = Chronic Kidney Disease
HF = Heart Failure
DSMES = Diabetes Self-Management Education and Support
SMBG = Self-Monitored Blood Glucose

Fig. 1 Decision cycle for patient-centred glycaemic management in type 2 diabetes

Table 2 Glucose-lowering medications and therapies available in the USA or Europe and specific characteristics that may guide individualised treatment choices in non-pregnant adults with type 2 diabetes

Class	Medications/therapies in class	Primary physiological action(s)	Advantages	Disadvantages/adverse effects	Efficacy
Lifestyle					
Diet quality	<ul style="list-style-type: none"> • Mediterranean type • DASH • Low carbohydrate • Vegetarian • Others 	<ul style="list-style-type: none"> • Depends on diet 	<ul style="list-style-type: none"> • Inexpensive • No side effects 	<ul style="list-style-type: none"> • Requires instruction • Requires motivation • Requires lifelong behavioural change • Social barriers may exist 	Intermediate
Physical activity	<ul style="list-style-type: none"> • Running, walking • Bicycling (including stationary) • Swimming • Resistance training • Yoga • Tai chi • Many others 	<ul style="list-style-type: none"> • Energy expenditure • Weight management • ↑ Insulin sensitivity 	<ul style="list-style-type: none"> • Inexpensive • ↓ Fall risk by increasing balance/strength • ? Improves mental health • ↑ Bone density • ↓ Blood pressure • ↓ Weight • Improves ASCVD risk factors 	<ul style="list-style-type: none"> • Risk of musculoskeletal injury • Requires motivation • Risk of foot trauma in patients with neuropathy • Requires lifelong behavioural change 	Intermediate
Energy restriction	<ul style="list-style-type: none"> • Individual energy restriction with or without energy tracking • Programmes with counselling • Food substitution programmes 	<ul style="list-style-type: none"> • Energy restriction • Weight management • ↓ Hepatic and pancreatic fat • ↑ Insulin sensitivity 	<ul style="list-style-type: none"> • Lowers glycaemia • Reduces need for diabetes and other medications • No serious side effects • Improves ASCVD risk factors 	<ul style="list-style-type: none"> • Requires motivation • Requires lifelong behavioural change 	Variable, with potential for very high efficacy; often intermediate
Oral medications					
Biguanides	<ul style="list-style-type: none"> • Metformin 	<ul style="list-style-type: none"> • ↓ Hepatic glucose production • Multiple other non-insulin-mediated mechanisms 	<ul style="list-style-type: none"> • Extensive experience • No hypoglycaemia • Inexpensive 	<ul style="list-style-type: none"> • GI symptoms • Vitamin B₁₂ deficiency • Use with caution or dose adjustment for CKD stage 3B (eGFR 30–44 ml min⁻¹ [1.73 m]⁻²) • Lactic acidosis (rare) 	High
SGLT2 inhibitors	<ul style="list-style-type: none"> • Canagliflozin • Dapagliflozin • Empagliflozin • Ertugliflozin 	<ul style="list-style-type: none"> • Blocks glucose reabsorption by the kidney, increasing glucosuria • ? Other tubulo-glomerular effects 	<ul style="list-style-type: none"> • No hypoglycaemia • ↓ Weight • ↓ Blood pressure • Effective at all stages of T2DM with preserved glomerular function • ↓ MACE, HF, CKD with some agents (see text) 	<ul style="list-style-type: none"> • Genital infections • UTI • Polyuria • Volume depletion/hypotension/dizziness • ↑ LDL-C • ↑ Creatinine (transient) • Dose adjustment/avoidance for renal disease • ↑ Risk for amputation (canagliflozin) • ↑ Risk for fracture (canagliflozin) • ↑ Risk for DKA (rare) • Fournier's gangrene (rare) • Expensive 	Intermediate–high (dependent on GFR)

Table 2 (continued)

Class	Medications/therapies in class	Primary physiological action(s)	Advantages	Disadvantages/adverse effects	Efficacy
DPP-4 inhibitors	<ul style="list-style-type: none"> • Sitagliptin • Vildagliptin^a • Saxagliptin • Linagliptin • Alogliptin 	<ul style="list-style-type: none"> • Glucose dependent: ↑ Insulin secretion • ↓ Glucagon secretion 	<ul style="list-style-type: none"> • No hypoglycaemia • Weight neutral • Well tolerated 	<ul style="list-style-type: none"> • Rare urticaria/angioedema • ↑ HF hospitalisation (saxagliptin) • Dose adjustment/avoidance for renal disease depending on agent • ? Pancreatitis • ? Arthralgia • ? Bullous pemphigoid • Expensive (USA); variable in Europe 	Intermediate
Sulfonylureas	<ul style="list-style-type: none"> • Glibenclamide/glyburide • Glipizide • Gliclazide^a • Glimepiride 	<ul style="list-style-type: none"> • ↑ Insulin secretion 	<ul style="list-style-type: none"> • Extensive experience • ↓ Microvascular risk (UKPDS) • Inexpensive 	<ul style="list-style-type: none"> • Hypoglycaemia • ↑ Weight • Uncertain cardiovascular safety • Dose adjustment/avoidance for renal disease • High rate of secondary failure 	High
TZDs	<ul style="list-style-type: none"> • Pioglitazone • Rosiglitazone^b 	<ul style="list-style-type: none"> • ↑ Insulin sensitivity 	<ul style="list-style-type: none"> • Low risk for hypoglycaemia • Durability • ↑ HDL-C • ↓ Triacylglycerols (pioglitazone) • ↓ ASCVD events (pioglitazone: in a post-stroke insulin-resistant population and as secondary endpoint in a high-CVD-risk diabetes population) • Lower cost 	<ul style="list-style-type: none"> • ↑ Weight • Oedema/heart failure • Bone loss • ↑ Bone fractures • ↑ LDL-C (rosiglitazone) • ? Bladder cancer • ? Macular oedema 	High
Meglitinides (Glinides)	<ul style="list-style-type: none"> • Repaglinide • Nateglinide 	<ul style="list-style-type: none"> • ↑ Insulin secretion 	<ul style="list-style-type: none"> • ↓ Postprandial glucose excursions • Dosing flexibility • Safe in advanced renal disease with cautious dosing (especially repaglinide) • Lower cost 	<ul style="list-style-type: none"> • Hypoglycaemia • ↑ Weight • Uncertain cardiovascular safety • Frequent dosing schedule 	Intermediate—high
α-Glucosidase inhibitors	<ul style="list-style-type: none"> • Acarbose • Miglitol 	<ul style="list-style-type: none"> • Slows carbohydrate digestion/absorption 	<ul style="list-style-type: none"> • Low risk for hypoglycaemia • ↓ Postprandial glucose excursions • Non-systemic mechanism of action • Cardiovascular safety • Lower cost 	<ul style="list-style-type: none"> • Frequent GI side effects • Frequent dosing schedule • Dose adjustment/avoidance for renal disease 	Low–intermediate
Bile acid sequestrants	<ul style="list-style-type: none"> • Colesevelam^b 	<ul style="list-style-type: none"> • ? ↓ Hepatic glucose production • ? ↑ Incretin levels 	<ul style="list-style-type: none"> • No hypoglycaemia • ↓ LDL-C 	<ul style="list-style-type: none"> • Constipation • ↑ Triacylglycerols • May ↓ absorption of other medications • Intermediate expense 	Low–intermediate
Dopamine-2 agonists	<ul style="list-style-type: none"> • Quick-release bromocriptine^b 	<ul style="list-style-type: none"> • Modulates hypothalamic regulation of metabolism • ↑ Insulin sensitivity 	<ul style="list-style-type: none"> • No hypoglycaemia • ? ↓ ASCVD events 	<ul style="list-style-type: none"> • Headache/dizziness/syncope • Nausea • Fatigue • Rhinitis • High cost 	Low–intermediate

Table 2 (continued)

Class	Medications/therapies in class	Primary physiological action(s)	Advantages	Disadvantages/adverse effects	Efficacy
Injectable medications					
Insulins					
Long acting (basal)	<ul style="list-style-type: none"> • Degludec (U100, U200) • Detemir • Glargine (U100, U300) 	<ul style="list-style-type: none"> • Activates insulin receptor • ↑ Glucose disposal • ↓ Glucose production 	<ul style="list-style-type: none"> • Nearly universal response • Theoretically unlimited efficacy • Once daily injection 	<ul style="list-style-type: none"> • Hypoglycaemia • Weight gain • Training requirements • Frequent dose adjustment for optimal efficacy • High cost 	Very high
Intermediate acting (basal)	<ul style="list-style-type: none"> • Human NPH 	<ul style="list-style-type: none"> • Activates insulin receptor • ↑ Glucose disposal • ↓ Glucose production 	<ul style="list-style-type: none"> • Nearly universal response • Theoretically unlimited efficacy • Less expensive than analogues 	<ul style="list-style-type: none"> • Hypoglycaemia • Weight gain • Training requirements • Often given twice daily • Frequent dose adjustment for optimal efficacy 	Very high
Rapid acting	<ul style="list-style-type: none"> • Aspart (conventional and fast-acting) • Lispro (U100, U200) • Glulisine 	<ul style="list-style-type: none"> • Activates insulin receptor • ↑ Glucose disposal • ↓ Glucose production 	<ul style="list-style-type: none"> • Nearly universal response • Theoretically unlimited efficacy • ↓ Postprandial glucose 	<ul style="list-style-type: none"> • Hypoglycaemia • Weight gain • Training requirements • May require multiple daily injections • Frequent dose adjustment for optimal efficacy • High cost 	Very high
Inhaled rapid acting	<ul style="list-style-type: none"> • Human insulin inhalation powder^b 	<ul style="list-style-type: none"> • Activates insulin receptor • ↑ Glucose disposal • ↓ Glucose production 	<ul style="list-style-type: none"> • Nearly universal response • ↓ Postprandial glucose • More rapid onset and shorter duration than rapid-acting analogues 	<ul style="list-style-type: none"> • Spirometry (FEV₁) required before initiating, after 6 months and annually • Contraindicated in chronic lung disease • Not recommended in smokers • Hypoglycaemia • Weight gain • Training requirements • May require multiple inhalations daily • Frequent dose adjustment for optimal efficacy; limited options in dosing interval • High cost • Respiratory side effects (e.g. bronchospasm, cough, decline in FEV₁) 	High
Short acting	<ul style="list-style-type: none"> • Human regular (U100, U500) 	<ul style="list-style-type: none"> • Activates insulin receptor • ↑ Glucose disposal • ↓ Glucose production 	<ul style="list-style-type: none"> • Nearly universal response • Theoretically unlimited efficacy • ↓ Postprandial glucose • Less expensive than analogues 	<ul style="list-style-type: none"> • Hypoglycaemia • Weight gain • Training requirements • Frequent dose adjustment for optimal efficacy • May require multiple daily injections 	Very high

Table 2 (continued)

Class	Medications/therapies in class	Primary physiological action(s)	Advantages	Disadvantages/adverse effects	Efficacy
Premixed	• Many	<ul style="list-style-type: none"> • Activates insulin receptor • ↑ Glucose disposal • ↓ Glucose production 	<ul style="list-style-type: none"> • Nearly universal response • Theoretically unlimited efficacy • Fewer injections than basal/bolus before every meal • Recombinant human analogues are less expensive 	<ul style="list-style-type: none"> • Hypoglycaemia • Weight gain • Training requirements • Frequent dose adjustment for optimal efficacy • High cost (except human insulin premix) • Can lead to obligate eating 	Very high
GLP-1 RA					
Shorter acting	<ul style="list-style-type: none"> • Exenatide • Lixisenatide 	<ul style="list-style-type: none"> • Glucose dependent: ↑ Insulin secretion • ↓ Glucagon secretion • Slows gastric emptying • ↑ Satiety 	<ul style="list-style-type: none"> • No hypoglycaemia as monotherapy • ↓ Weight • Excellent postprandial glucose efficacy for meals after injections • Improves cardiovascular risk factors 	<ul style="list-style-type: none"> • Frequent GI side effects that may be transient • Modestly ↑ heart rate • Training requirements • Dose adjustment/avoidance in renal disease • Acute pancreatitis (rare/uncertain) • Very high cost 	Intermediate–high
Longer acting	<ul style="list-style-type: none"> • Dulaglutide • Exenatide extended-release • Liraglutide • Semaglutide 	<ul style="list-style-type: none"> • Glucose dependent: ↑ Insulin secretion • ↓ Glucagon secretion • ↑ Satiety 	<ul style="list-style-type: none"> • No hypoglycaemia as monotherapy • ↓ Weight • ↓ Postprandial glucose excursions • Improves cardiovascular risk factors • ↓ MACE with some agents (see text) • ↓ Albuminuria with some agents (see text) • Greater lowering of fasting glucose vs short-acting preparations • Once weekly dosing (except liraglutide, which is daily) 	<ul style="list-style-type: none"> • GI side effects, including gall bladder disease • Greater ↑ heart rate • Training requirements • Dose adjustment/avoidance for some agents in renal disease • Acute pancreatitis (rare/uncertain) • C cell hyperplasia/medullary thyroid tumours (rare/uncertain; observed in animals only) • Very high cost 	High–very high
Other injectables					
Amylin mimetics	• Pramlintide ^b	<ul style="list-style-type: none"> • ↓ Glucagon secretion • Slows gastric emptying • ↑ Satiety 	<ul style="list-style-type: none"> • ↓ Postprandial glucose excursions • ↓ Weight 	<ul style="list-style-type: none"> • Hypoglycaemia • Frequent dosing schedule • Training requirements • Frequent GI side effects • Very high cost 	Intermediate
Fixed-dose combination of GLP-1 RA and basal insulin analogues	<ul style="list-style-type: none"> • Liraglutide/degludec • Lixisenatide/glargine 	<ul style="list-style-type: none"> • Combined activities of components 	<ul style="list-style-type: none"> • Enhanced glycaemic efficacy vs components • Reduced adverse effects (e.g. GI, hypoglycaemia) vs components 	<ul style="list-style-type: none"> • Less weight loss than GLP-1 receptor agonist alone • Very high cost 	Very high

Table 2 (continued)

Class	Medications/therapies in class	Primary physiological action(s)	Advantages	Disadvantages/adverse effects	Efficacy
Weight loss medications	<ul style="list-style-type: none"> • Lorcaserin^b • Naltrexone/bupropion • Orlistat • Phentermine/topiramate^b • Liraglutide 3 mg 	<ul style="list-style-type: none"> • Reduced appetite • Fat malabsorption (orlistat) 	<ul style="list-style-type: none"> • Mean 3–9 kg weight loss vs placebo 	<ul style="list-style-type: none"> • High discontinuation rates from side effects • <50% achieve ≥5% weight loss • Drug-specific side effects • Limited durability • High cost 	Intermediate
Metabolic surgery	<ul style="list-style-type: none"> • VSG • RYGB • Adjustable gastric band • BPD 	<ul style="list-style-type: none"> • Restriction of food intake (all) • Malabsorption (RYGB, BPD) • Changes in hormonal and possibly neuronal signalling (VSG, RYGB, BPD) 	<ul style="list-style-type: none"> • Sustained weight reduction • ↑ Rate of remission of diabetes • ↓ Number of diabetes drugs • ↓ Blood pressure • Improved lipid metabolism 	<ul style="list-style-type: none"> • High initial cost • ↑ Risk for early and late surgical complications • ↑ Risk for reoperation • ↑ Risk for dumping syndrome • ↑ Nutrient and vitamin malabsorption • ↑ Risk for new-onset depression • ↑ Risk for new-onset opioid use • ↑ Risk for gastroduodenal ulcer • ↑ Risk for hypoglycaemia • ↑ Risk for alcohol use disorder 	Very high

More details available in ADA's 'Standards of Medical Care in Diabetes—2018' [3]

Glucose-lowering efficacy of drugs by change in HbA_{1c}: >22 mmol/mol (2%) very high, 11–22 mmol/mol (1–2%) high, 6–11 mmol/mol (0.5–1.5%) intermediate, <6 mmol/mol (0.5%) low

^aNot licensed in the USA for type 2 diabetes

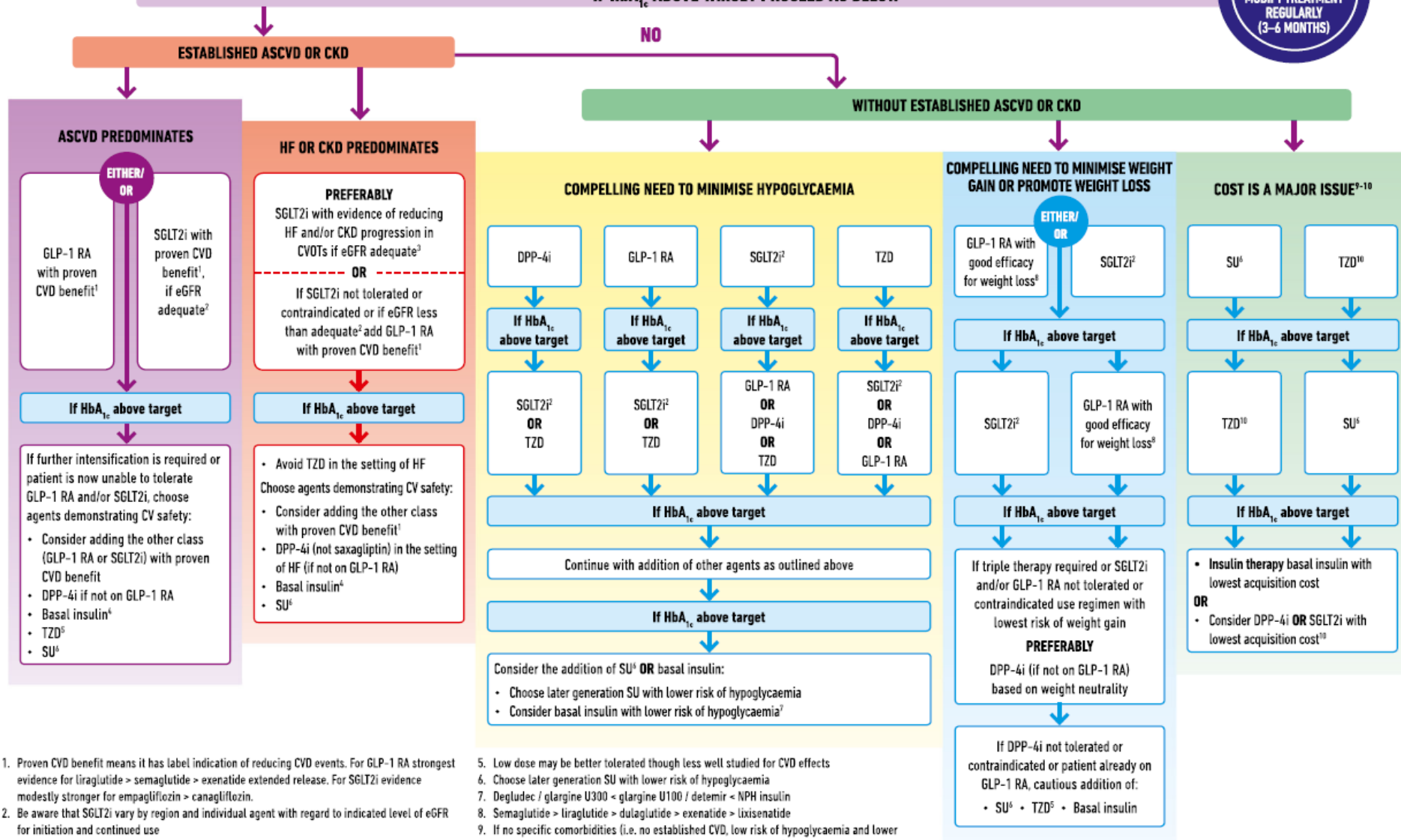
^bNot licensed in Europe for type 2 diabetes

BPD, biliopancreatic diversion; DASH, Dietary Approaches to Stop Hypertension; DKA, diabetic ketoacidosis; FEV₁, forced expiratory volume in 1 s on pulmonary function testing; GI, gastrointestinal; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; RYGB, Roux-en-Y gastric bypass; VSG, vertical sleeve gastrectomy; UTI, urinary tract infection

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH

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

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

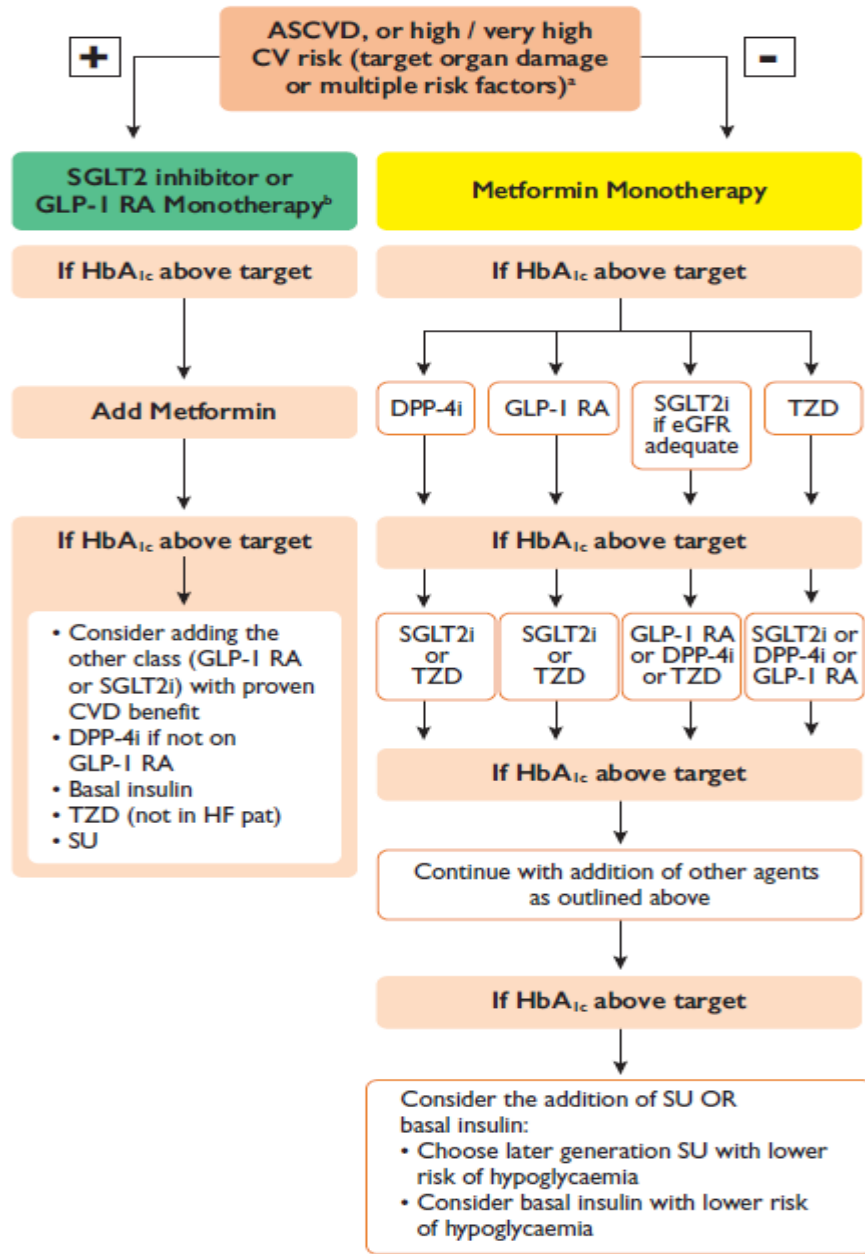


1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent 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 effects
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 hypoglycaemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

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

A Type 2 DM - Drug naïve patients



B Type 2 DM - On metformin

