UNIVERSITÀ DI FOGGIA

Gaetano Serviddio

LA FENOTIPIZZAZIONE NELLA SCELTA DELLA TERAPIA ANTIDIABETICA

Medicina Interna e dell'invecchiamento
Direttore: Prof. G. Vendemiale

Il sottoscritto Gaetano Serviddio

ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

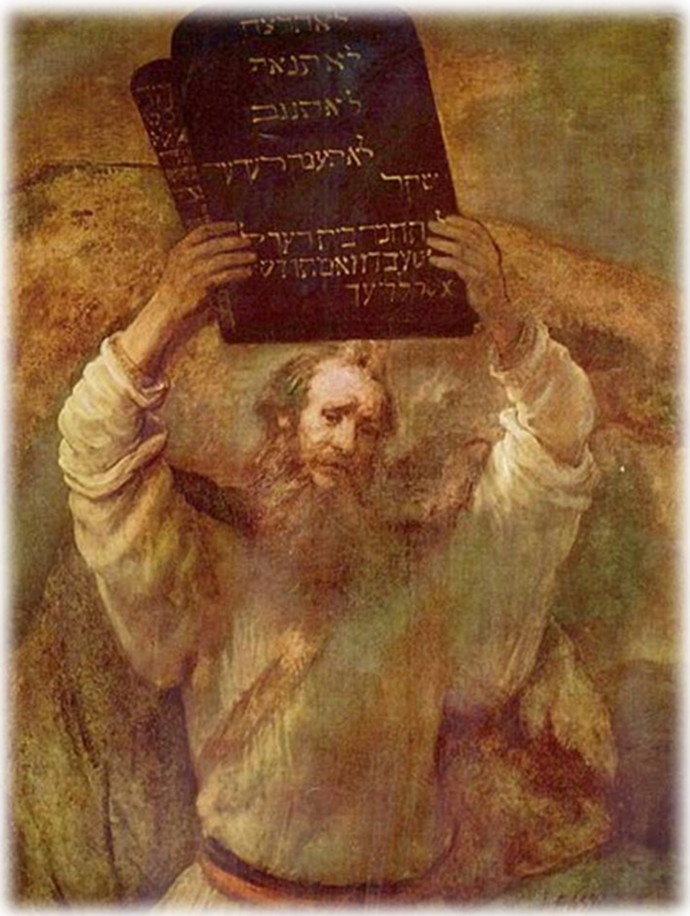
dichiara

☐ *che negli ultimi due anni NON ha avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario*

☒ *che negli ultimi due anni ha avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:*

- *Lilly*
- *Boehringer*
- *Astra-Zeneca*
- *Takeda*

Principi generali



''Mosè con le tavole della legge'', Rembrandt – Staatliche Museen, Berlino

1. Modificare lo **stile di vita**
2. Evitare **l'ipoglicemia**
3. Contrastare **l'aumento di peso**
4. HbA1c ottimale è **≤ 6,5% (7% per ADA)** o il più **più sicuro ottenibile**
5. **Individualizzare** ogni target glicemico (HbA1c, FPG, PPG)

2018 AACE/ACE T2D Management, Endocr Pract. 2018

Chi abbiamo di fronte?

Anziano sano (poche e nessuna comorbilità, stato funzionale e cognitivo integro)

- **Aspettativa di vita lunga**
- **Glicata <7,5% (58mmol/mol)**
- **Glicemia a digiuno <130mg/dL**
- **Glicemia post-prandiale > 150mg/dL**

Anziano complesso/rischio intermedio

- Aspettativa di vita intermedia
- **Glicata <8% (58mmol/mol)**
- **Glicemia a digiuno <150mg/dL**
- **Glicemia post-prandiale > 180mg/dL**

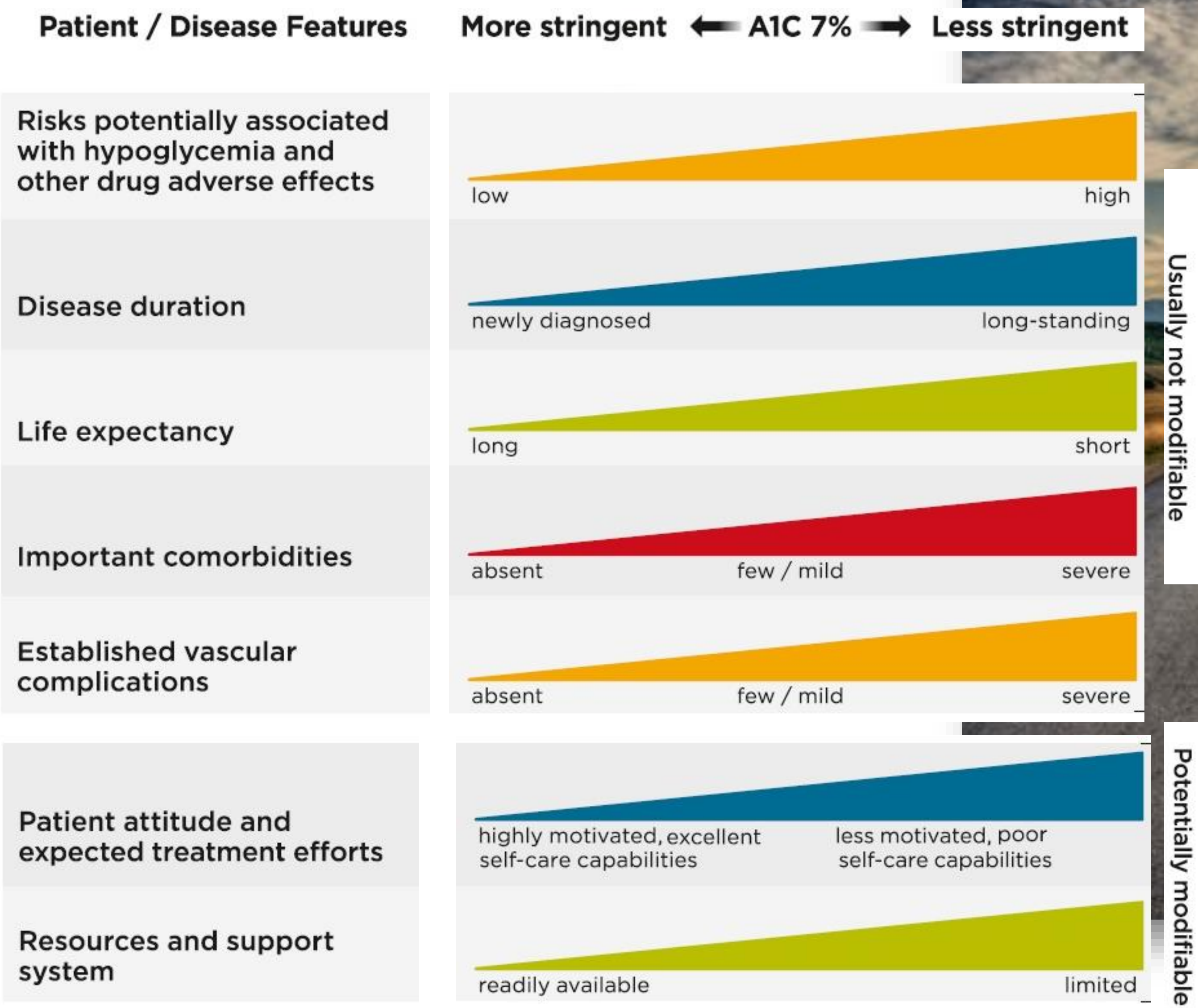
- Older adults who are functional, are cognitively intact, and have significant life expectancy should receive diabetes care using goals developed for younger adults.

Anziano molto complesso/rischio intermedio

- Aspettativa di vita bassa
- Alto rischio ipoglicemie
- **Glicata <8,5% (58mmol/mol)**
- **Glicemia a digiuno <180mg/dL**
- **Glicemia post-prandiale > 200mg/dL**

Diabetes Care Volume 41, Supplement 1, January 2018

Decidere il target..



ADA, Standards Of Medical Care In Diabetes, 2018

Come raggiungere il target...

AACE/ACE Consensus Statement

CONSENSUS STATEMENT BY THE AMER
CLINICAL ENDOCRINOLOGISTS AND AI
ENDOCRINOLOGY ON THE COMPREHEN
MANAGEMENT ALGORITHM – *2018 EX*

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This document represents the official position of the American Associat College of Endocrinology. Where there were no randomized controlled trial in clinical practice, the participating clinical experts utilized their judgmen achieve consensus among the committee members. Position statements are be considered prescriptive for any individual patient and cannot replace th

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[13]Chairman, (Medicine and School of M William Beau First Faculty c President, An Elect, Americ Investigator, M Committee, T Washington S Medicine, Uni The Center fo of Medicine, Washington U Director, The Health at Mo Cardiology ar of Medicine a of Endocrino Endocrinolog Specialists, Ed Professor, Me University C Co-Director, I California; [20]P Director, End Address co Endocrinologi E-mail: public To purchase r Copyright © 2

ENDOCRI

Diabetologia
https://doi.org/10.1007/s00125-018-4729-5

CONSENSUS REPORT

Management of hyperglycaemia in type 2 diab
report by the American Diabetes Association (A
Association for the Study of Diabetes (EASD)

Melanie J. Davies[1,2] · David A. D'Alessio[3] · Judith Fradkin[4] · Walter N. K
Geltrude Mingrone[7,8] · Peter Rossing[9,10] · Apostolos Tsapas[11] · Debora

Abstract

The American Diabetes Association and the European Association for the Stud position statements, published in 2012 and 2015, on the management of type 2 literature since 2014 informed new recommendations. These include additiona management education and support. For those with obesity, efforts targeting wei interventions, are recommended. With regards to medication management, for pa glucose cotransporter-2 (SGLT2) inhibitor or a glucagon-like peptide-1 (GLP-1) r recommended. For patients with chronic kidney disease or clinical heart failure a inhibitor with proven benefit is recommended. GLP-1 receptor agonists are gene

Keywords Cardiovascular disease · Chronic kidney disease · Costs · Gluco Hypoglycaemia · Patient-centred care · Type 2 diabetes mellitus · Weight man

Abbreviations

ARR	Absolute risk reduction
ASCVD	Atherosclerotic cardiovascular disease
CANVAS	Canagliflozin Cardiovascular Assessment Study
CKD	Chronic kidney disease
CVD	Cardiovascular disease
CVOT	Cardiovascular outcomes trial
DKA	
DPP-4	
DPP-4i	
DSMES	
EMPA-REG	
ESRD	
EXSCEL	
GLP-1	
GLP-1 RA	
HF	
LEADER	
MACE	
MI	
MNT	
RCT	
SGLT2	

M. J. Davies and J. B. Buse were co-chairs for the Consensus Statement Writing Group. D. A. D'Alessio, J. Fradkin, W. N. Kernan and D. J. Wexler were the writing group members for the ADA. C. Mathieu, G. Mingrone, P. Rossing and A. Tsapas were writing group members for the EASD.

This article is being simultaneously published in *Diabetes Care* and *Diabetologia* by the American Diabetes Association and the European Association for the Study of Diabetes.

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Extended author information available on the last page of the article

Published online: 05 October 2018

AMD ASSOCIAZIONE MEDICI DIABETOLOGI 1974

SID Società Italiana di Diabetologia

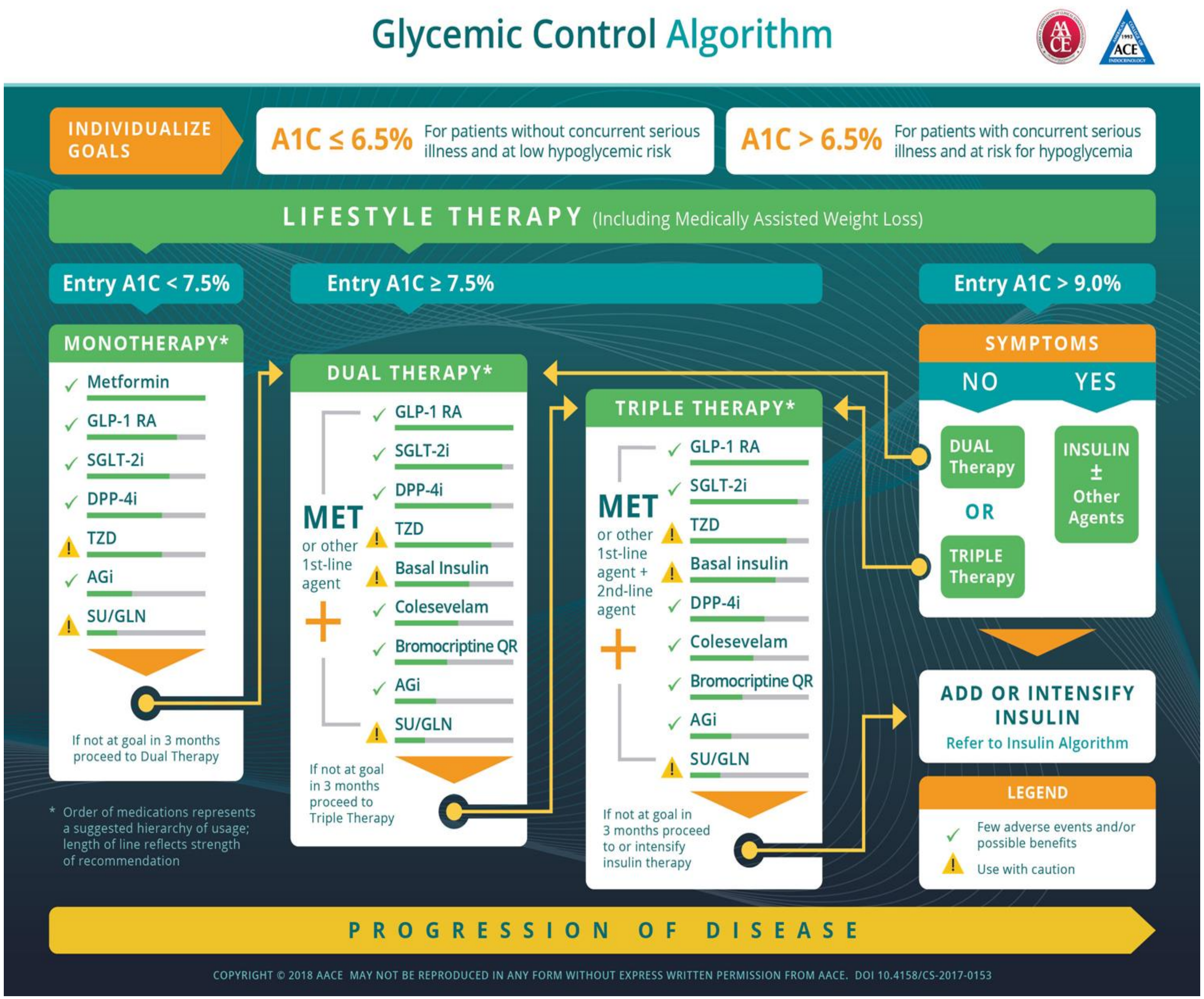
Standard italiani per la cura del diabete mellito 2018

Questo testo è disponibile in forma elettronica presso i siti istituzionali di AMD e SID

Data di rilascio: 27 aprile 2018

Si ricorda che è sempre responsabilità del medico curante, in base alle proprie esperienze e nel rispetto della normativa vigente e della deontologia professionale, determinare la cura migliore per il paziente. Per le indicazioni terapeutiche, la posologia, i modi di somministrazione e per le altre caratteristiche delle singole specialità medicinali citate, fare riferimento ai rispettivi riassunti delle caratteristiche di prodotto autorizzati. I medici sono invitati a contattare le rispettive aziende produttrici per qualsiasi domanda o limitazione dei farmaci. Tutti i soggetti coinvolti nella stesura del presente documento non assumono responsabilità alcuna per danni e quant'altro a persone o cose imputabili in qualsiasi maniera e/o per qualsiasi ragione all'uso delle informazioni contenute in questa pubblicazione e/o per eventuali errori od omissioni in essa contenuti nonostante gli sforzi profusi al fine di garantire un'informazione la più corretta possibile e pienamente aderente allo stato delle conoscenze medico-scientifiche attuali. Tutti i partecipanti all'iniziativa sono consapevoli che, pur avendo curato in ogni particolare i contenuti proposti, possono essere incorsi in sviste o errori, di cui si scusano in anticipo e per i quali ringraziano per le segnalazioni del caso. Nessun soggetto terzo, al di fuori dei partecipanti a questa iniziativa, ha avuto ruolo alcuno nella progettazione, ideazione, sviluppo, realizzazione e gestione dei contenuti qui proposti. L'intero documento è protetto da qualsiasi influenza commerciale.

Come raggiungere il target...



Il target su efficacia non è funzionale

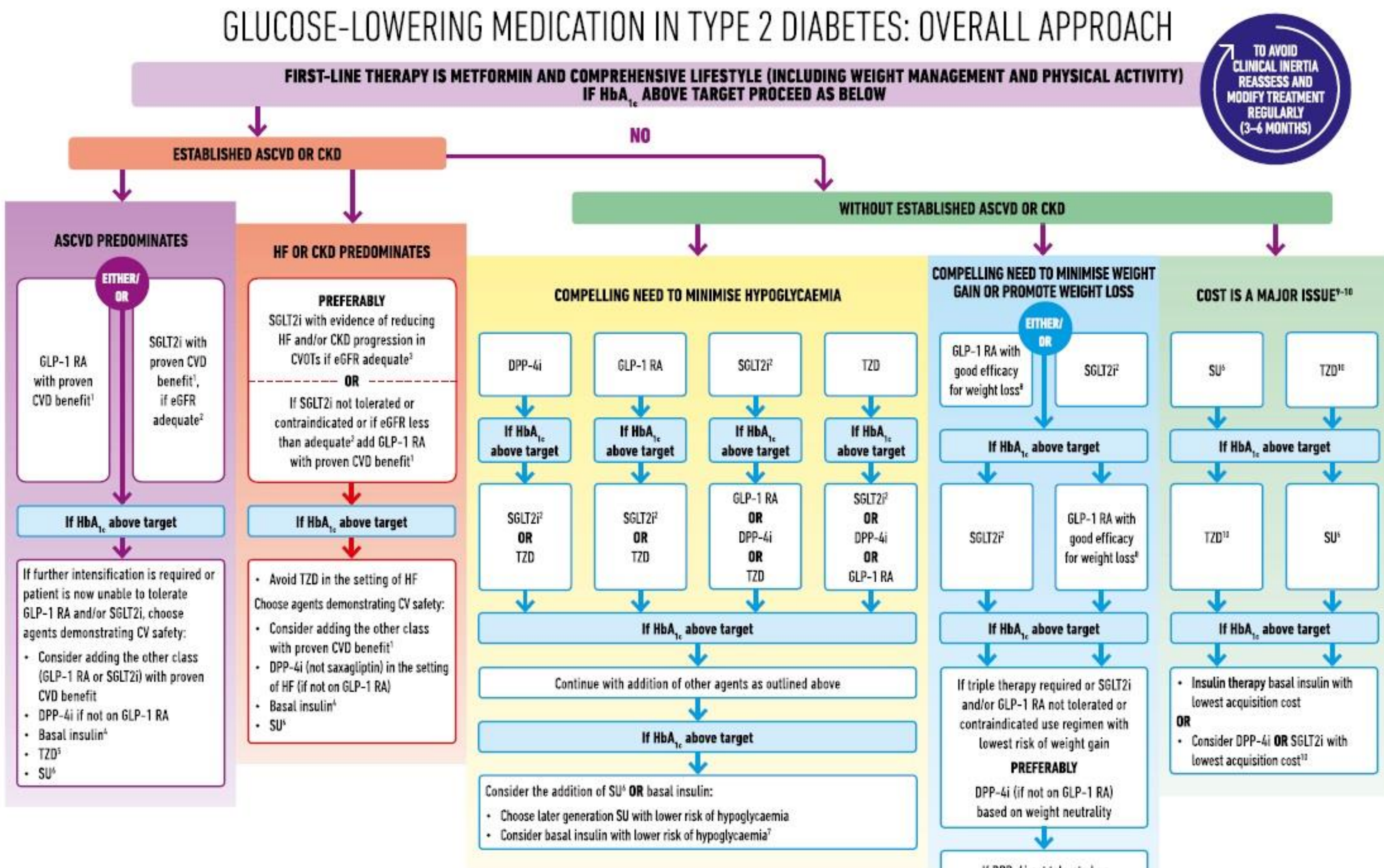
Standard italiani per la cura del diabete mellito 2018

Tabella 4.H2. Benefici dei farmaci per il diabete di tipo 2.

	Metformina	Acarbose	GLP1RA	Gliflozine	Gliptine	Pioglitazone	SU/glinidi
Riduzione HbA1c a breve termine (3-4 mesi)*	+++	+	+++	++	++	+	+++
Riduzione HbA1c a medio termine (1-2 anni)*	++	+	+++	++	++	++	++
Riduzione HbA1c a lungo termine (oltre 2 anni)*	++	+	+++	++	ND	+++	+
Riduzione peso corporeo	+/-	+/-	+++	++	-	-	-

AMD-SID – Standard italiani per la cura del diabete mellito 2018

Come raggiungere il target...



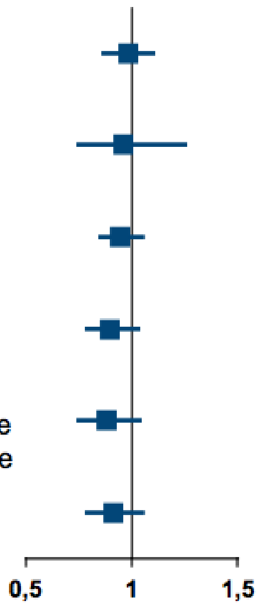
1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent 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

L'evoluzione della fenotipizzazione

alla sartorialità...

‘Older’ glucose-lowering agents have not definitively shown positive effects on major CV events …

Trial	Outcome	HR (95% CI)
ACE (N=6522)[1] **Acarbose versus placebo + CV prevention therapy**	5P-MACE: CV death, NF-MI, NF-stroke, hUA, hHF	0.98 (0.86, 1.11)
TOSCA.IT (N=3,028)[2] **PIO versus SU as add-on to MET**	All-cause death, NF-MI, silent MI, NF-stroke, urgent coronary revascularization	0.96 (0.74, 1.26)
ADVANCE (N=11,140)[3] **HbA_{1c} ≤6.5% versus HbA_{1c} >6.5% (gliclazide + any other agent)**	3P-MACE: CV death, NF-MI, NF-stroke	0.94 (0.84, 1.06)
ACCORD (N=10,251)[4] **HbA_{1c} <6.0% versus HbA_{1c} 7.0–7.9% (MET, SU, TZD, insulin)**	3P-MACE: CV death, NF-MI, NF-stroke	0.90 (0.78, 1.04)
VADT (N=1791)[5] **HbA_{1c} –1.5% versus the standard group (MET or GLIM, ROSI, insulin)**	7P-MACE: CV death, MI, stroke, HF, surgery for vascular disease, inoperable CHD, amputation for ischemic gangrene	0.88 (0.74, 1.05)
DEVOTE (N=7367)[6] **IGlar versus IDeg**	3P-MACE: CV death, NF-MI, NF-stroke	0.91 (0.78, 1.06)



CI, confidence interval; CV, cardiovascular; GLIM, glimepiride; HR, hazard ratio; MACE, major adverse cardiovascular event; hHF, hospitalization for heart failure; HF, heart failure; hUA, hospitalization for unstable angina; MET, metformin; NF, non-fatal; PIO, pioglitazone; ROSI, rosiglitazone; SU, sulfonylurea; TZD, thiazolidinedione

1. Holman RR, et al. *Lancet Diabetes Endocrinol* 2017; doi: 10.1016/S2213-8587(17)30318-2; 2. Vaccaro O, et al. *Lancet Diabetes Endocrinol* 2017;5:887–897; 3. ADVANCE Collaborative Group. *N Engl J Med* 2008;358:2560–2572; 4. The ACCORD Study Group. *N Engl J Med* 2008;358:2545–2559; 5. Duckworth W, et al. *N Engl J Med* 2009;360:129–139; 6. Marso SP, et al. *N Engl J Med* 2017;377:723–732

DPP4-i trials: SAVOR-TIMI, EXAMINE, TECOS

Clinical Trial	DPP-4 Inhibitor Daily Dose*	DPP-4i vs Placebo, N	History of CV Disease Patients, %	Median Follow-Up Years	Primary CV Composite Outcome†	Myocardial Infarction (Fatal or Nonfatal)	Stroke (Fatal or Nonfatal)	CV Mortality	All-Cause Mortality	Hospitalization for Heart Failure
SAVOR-TIMI 53[50]	Saxagliptin 5 mg	8280 vs 8212	78	2.1	1.00 (0.89–1.12)	0.95 (0.80–1.12)	1.11 (0.88–1.39)	1.03 (0.87–1.22)	1.11 (0.96–1.27)	1.27 (1.07–1.51)
EXAMINE[49]	Alogliptin 25 mg	2701 vs 2679	100	1.5	0.96 (≤1.16)‡	1.08 (0.88–1.33)	0.95 (≤1.14)‡	0.85 (0.66–1.10)	0.88 (0.71–1.09)	1.07 (0.79–1.46)
TECOS[51]	Sitagliptin 100 mg	7257 vs 7266	100	3.0	0.98 (0.89–1.08)	0.95 (0.81–1.11)	0.97 (0.79–1.19)	1.03 (0.89–1.19)	1.01 (0.90–1.14)	1.00 (0.83–1.20)
Meta-analyses Xu et al[44]; Mahmoud et al[47]; Abbas et al[48]	Saxagliptin 5 mg; Alogliptin 25 mg; Sitagliptin 100 mg	18313 vs 18230	78–100	1.5–3.0	0.991 (0.929–1.057)	0.98 (0.88–1.09	1.00 (0.86–1.17)	1.01 (0.91–1.12)	1.03 (0.95–1.11)	1.12 (1.00–1.26)

Results are expressed by hazard ratio or odds ratio (with 95% confidence intervals). CV indicates cardiovascular; DPP-4, dipeptidyl peptidase-4 EXAMINE, Examination of Cardiovascular Outcomes: Alogliptin vs. Standard of Care in Patients With Type 2 Diabetes Mellitus and Acute Coronary Syndrome; SAVOR-TIMI, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53; and TECOS, Trial Evaluating Cardiovascular Outcomes With Sitagliptin.

*Reduction of daily dose if necessary according to estimated glomerular filtration rate.

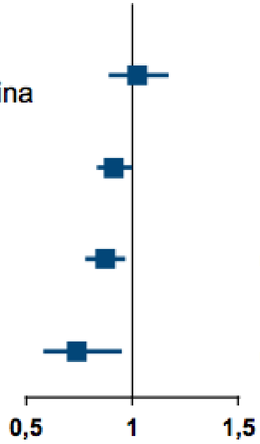
†Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

‡Upper boundary of the 1-sided repeated confidence interval.

Scheen A. J. Et al, Circulation Research, 2018

GLP-1 RAs: ELIXA, EXCEL, LEADER, SUSTAIN 6

Trial	Outcome	HR (95% CI)
ELIXA (N=6068)[1] Lixisenatide vs placebo	Time to first occurrence of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina	1.02 (0.89, 1.17)
EXSCEL (N=14,752)[2] Exenatide vs placebo	3P-MACE: CV death, NF-MI, NF-stroke	0.91 (0.83, 1.00)
LEADER (N=9340)[3] Liraglutide vs placebo	3P-MACE: CV death, NF-MI, NF-stroke	0.87 (0.78, 0.97)
SUSTAIN-6 (N=3297)[4] Semaglutide vs placebo	3P-MACE: CV death, NF-MI, NF-stroke	0.74 (0.58, 0.95)



CI, confidence interval; CV, cardiovascular; CVOT, cardiovascular outcomes trial; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; MI, myocardial infarction; NF, nonfatal; 3P-MACE. 3 point major adverse cardiac event

1. Pfeffer MA, et al. *N Engl J Med* 2015;373:2247–2257; 2. Holman RR, et al. N Engl J Med 2017;377:1228–1239; 3. Marso SP, et al. *N Engl J Med* 2016;375:311–322; 4. Marso SP, et al. *N Engl J Med* 2016;375:1834–1844

Altri trial sono in arrivo

Rosenstock *et al. Cardiovasc Diabetol (2018) 17:39*
https://doi.org/10.1186/s12933-018-0682-3

Cardiovascular Diabetology

ORIGINAL INVESTIGATION Open Access

CrossMark

Rationale, design, and baseline characteristics of the C and Renal Microvascu with LINAgliptin (CARI double-blind, placebo in patients with type 2 cardio-renal risk

Julio Rosenstock[1*], Vlado Perkovic[2], John H. Alexan
Robert D. Toto[6], Christoph Wanner[7], Bernard Zinm
Uli C. Broedl[11], Hans-Juergen Woerle[12], Jyothis T. G
on behalf of CARMELINA® investigators

Clinical Trial Design

Diabetes & Vascular Disease Research
2015, Vol. 12(3) 164–174
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DOI: 10.1177/1479164115570301
dvr.sagepub.com
SAGE

Design and baseline characteristics of the CARdiovascular Outcome Trial of LINAgliptin Versus Glimepiride in Type 2 Diabetes (CAROLINA®)

**Nikolaus Marx[1], Julio Rosenstock[2],
Zinman[4,5], John J Kastelein[6], John N
Erich Bluhmki[9], Michaela Mattheus
Patel[12], Odd Erik Johansen[13] and H**

Abstract
CARdiovascular Outcome Trial of LINAgliptin
randomized trial in subjects with early type 2 dia
will determine the long-term cardiovascular im
were sulphonylurea-naïve with HbA_{1c} 6.5%–8.
combination regimen <5 years) with HbA_{1c} 6.5
death, non-fatal myocardial infarction, non-fata
with primary outcome events will be required
safety by comparing the upper limit of the two-s
Hierarchical testing for superiority will follow, a
risk reduction. A total of 6041 patients were tre
HbA1c 7.2%, 66% on 1 and 24% on 2 glucose-
The results of CARdiovascular Outcome Trial
decision-making process for selecting a second

American Heart Journal 200 (2018) 83–89

Contents lists available at ScienceDirect

American Heart Journal

ELSEVIER

AHJ

Trial Design

The design and rationale for the Dapagliflozin Effect on Cardiovascular Events (DECLARE)–TIMI 58 Trial

Check for updates

Stephen D. Wiviott [a,*], Itamar Raz [b], Marc P Bonaca [a], Ofri Mosenzon [b], Eri T Kato [c], Avivit Cahn [b], Michael G Silverman [d], Sameer Bansilal [e], Deepak L Bhatt [a], Lawrence A. Leiter [g], Darren K. McGuire [i], John PH Wilding [h], Ingrid AM Gause-Nilsson [f], Anna Maria Langkilde [f], Peter A. Johansson [f], Marc S. Sabatine [a]

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Target renale...

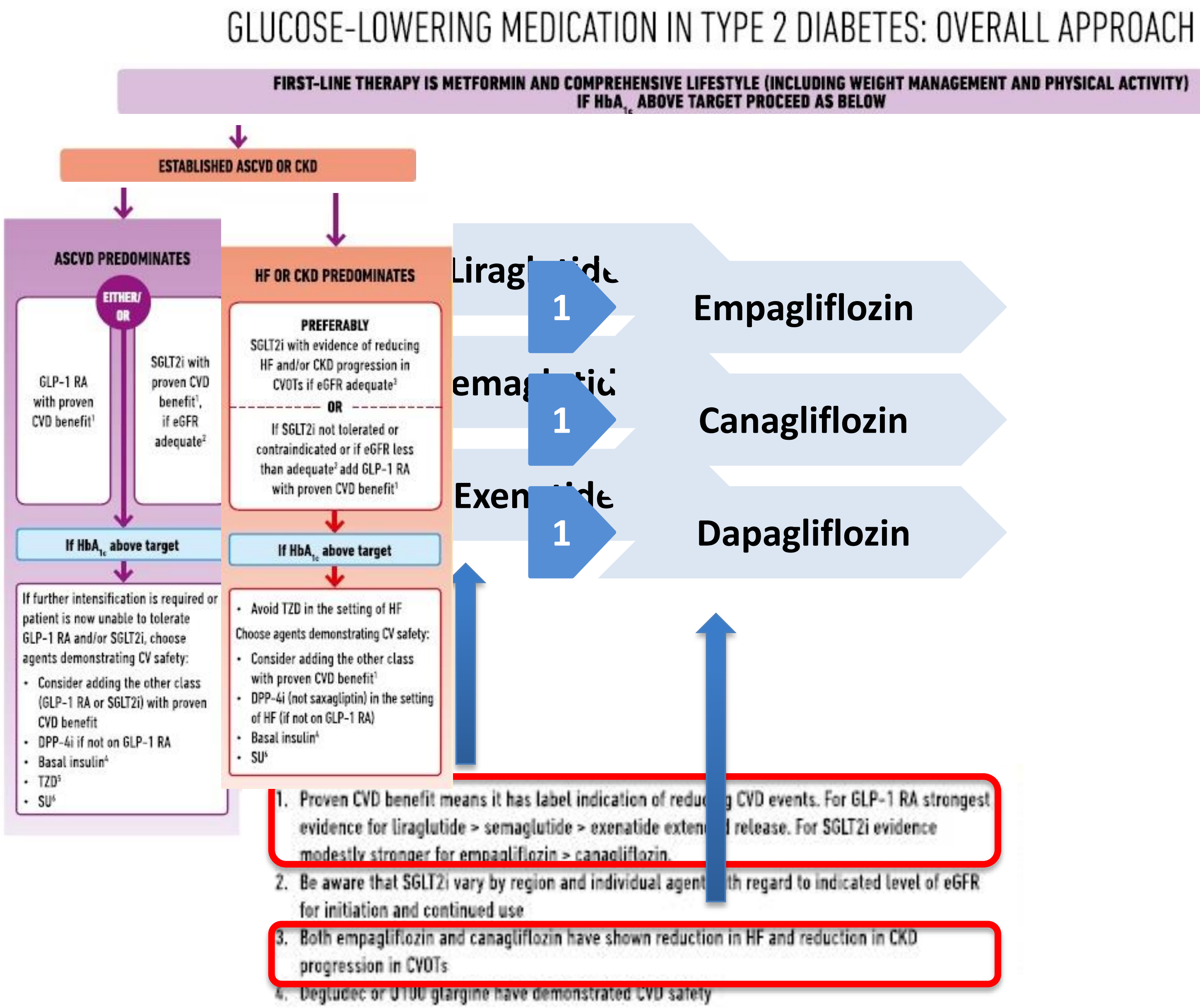
Table 1. Antidiabetic drugs and renal outcome endpoints

Drug class	Substance	Ref	Comparator	Composite (renal/micro-vascular) endpoint	Composite endpoint outcome	New-onset DKD	UAE/UACR ≥30 mg/g	UAE/UACR >300 mg/g	Fall in GFR	ESKD RRT	Death from renal cause	Death from any cause
Biguanides	Metformin	12	Various	Y	+	–	–	–	n t	n t	–	++
		19	Sulfonyl-urea	Y	++	n t	n t	n t	++	++	n t	++
Sulfonylureas	n a	20		n t	n t	n t	n t	n t	n t	n t	n t	n t
α-Glucosidase inhibitors	Acarbose	22	Metformin	N	n a	n t	++	n a	–	n a	n t	n t
Glitazones	Pioglitazone	26	Acarbose	N	n a	n t	–	–	–	n t	n t	n t
DPP4 inhibitors	Aloglipzin	29	Sitagliptine crossover	N	n a	n t	++	n t	–	n t	n t	n t
	Linagliptin	30	Placebo	N	n a	n t	++	n t	n t	n t	n t	n t
	Sitagliptin	31	None	N	n a	n t	++	n t	n t	n t	n t	n t
Incretin mimetics	Exenatide	36	Placebo, insulin	N	n a	n t	n t	n t	–	n t	n t	n t
		37	Glimepiride	N	n a	n t	++	n t	n t	n t	n t	n t
	Liraglutide	38	Placebo	Y	++	++	++	++	–	–	–	++
SGLT2 inhibitors	Empagliflozin	15	Placebo	Y	++	++	++	++	–	++	–	++
	Canagliflozin	40	Placebo	Y	++	++	n t	++	n t	n t	n t	–
	Dapagliflozin	42	Placebo	N	n a	n t	+	+	n t	n t	n t	n t
Insulin	Insulin ≥3 injections daily or pump	47	Insulin ≤2 injections daily	N	n a	++	n t	++	++	++	n t	n t
	Insulin metaanalysis	49	Various	Y	–	n t	n t	n t	–	n t	n t	–
	Insulin degludec	50	Insulin glargine	N	n a	n t	n t	n t	–	n t	n t	–
	Insulin detemir/glargine	51	Pioglitazone	N	n a	n t	n t	n t	–	n t	n t	n t

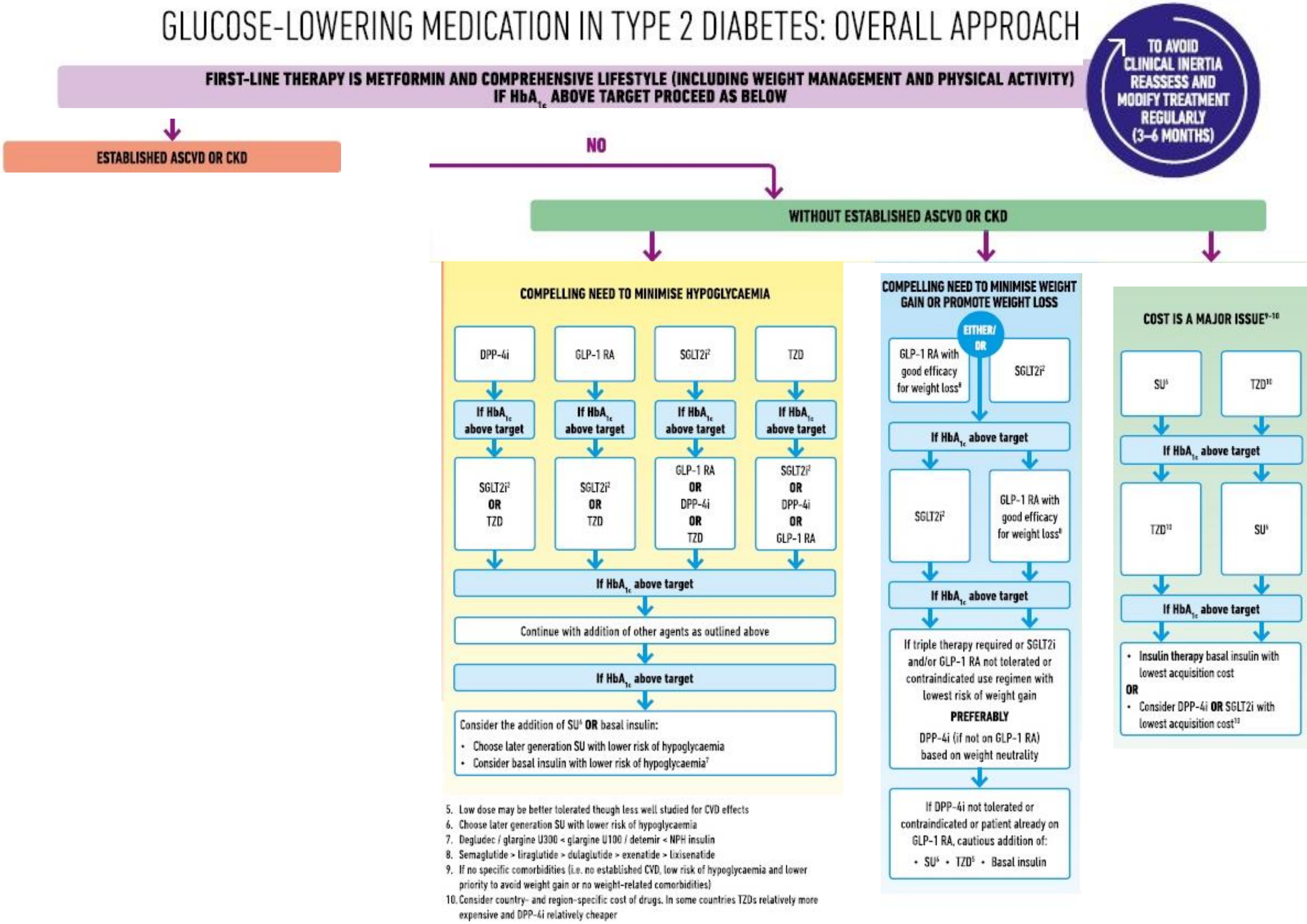
DKD, diabetic kidney disease; DPP4, dipeptidyl-peptidase-4; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; N, no; n a = not applicable; n t, not tested (and/or not reported); Ref, reference; RRT, renal replacement therapy; SGLT2, sodium-glucose-co-transporter 2; UACR, urinary albumin–creatinine ratio; UAE, urinary albumin excretion; Y, yes; –, no effect (or even negative effect); +, positive trend, not significant; ++, significant positive outcome (P at least <0.05). A "positive" (+) outcome meant improvement of a parameter (or a composite), or delay in progression, or a reduction of an event rate.

Prischl C. F. et al, Kidney Int Rep, 2018

Definito il target CVD, definire la miglior terapia



Come raggiungere il target...



LA FENOTIPIZZAZIONE PRIMA DI TUTTO...

“Saresti così gentile da indicarmi la strada per andar via di qui?”

“Dipende tutto da dove vuoi andare”, rispose lo Stregatto

“Non mi importa molto del dove” – disse Alice

“Allora non importa quale strada prenderai”

UNIVERSITÀ DI FOGGIA

Gaetano Serviddio

LA FENOTIPIZZAZIONE NELLA SCELTA DELLA TERAPIA ANTIDIABETICA

Medicina Interna e dell'invecchiamento
Direttore: Prof. G. Vendemiale