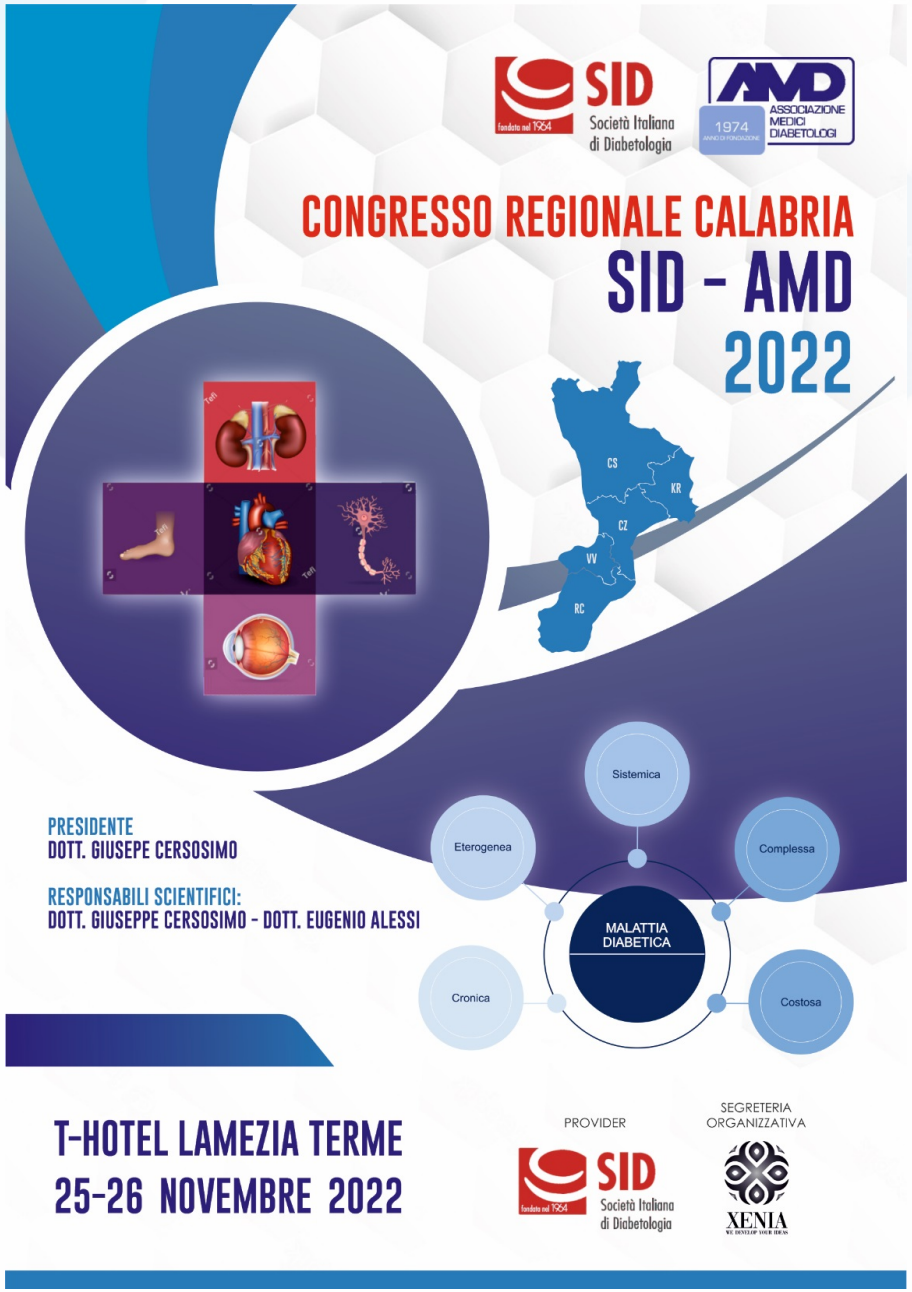


Diabete e Rene

Dott. Agata Mollica

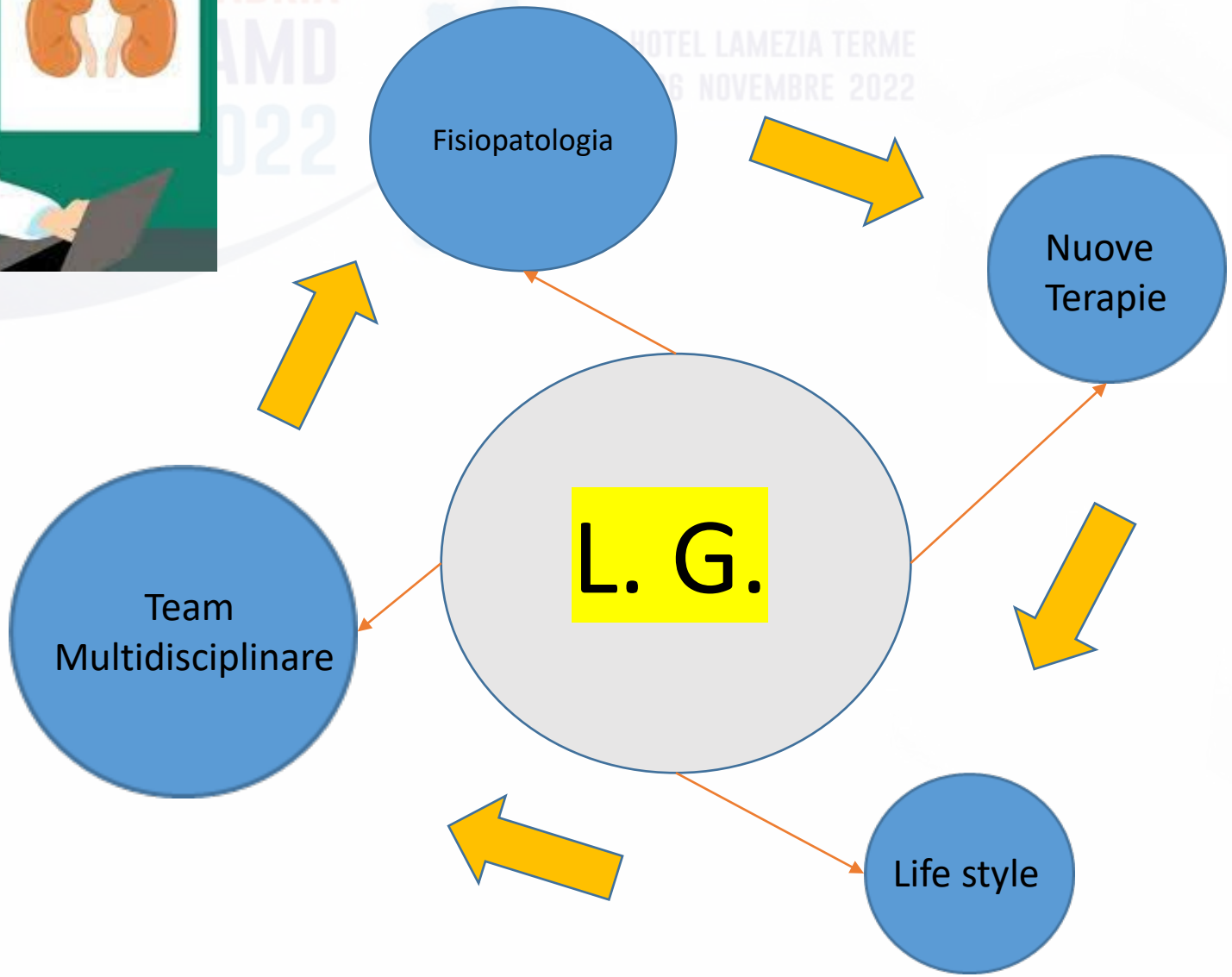
UOC Nefrologia e Dialisi abilitata al Trapianto
P. O. Annunziata – A. O. Cosenza
Direttore ff : Dott. T. Papalia

CONGRESSO REGIONALE CALABRIA
SID - AMD
2022

T-HOTEL LAMEZIA TERME
25-26 NOVEMBRE 2022

la dr./sa Agata MOLLICA dichiara di **NON** aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche

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.).


Fisiopatologia
Nuove Terapie
L. G.
Team Multidisciplinare
Life style

HD
DP
TX

CKD occurring among people with diabetes is common, morbid and costly.
The prevalence of diabetes around the world has reached epidemic proportions.
The International Diabetes Federation estimated that **537 million** people were living with diabetes in 2021.
This number is expected to increase to **784 million** by 2045.
The **prevalence of CKD** among people with diabetes is **>25%,** and it has been estimated that 40% of people with diabetes develop CKD during their lifetime, including a significant number who will develop kidney failure requiring dialysis or transplantation. As the prevalence of diabetes has increased, the prevalence ok CKD attributable to diabetes has grown proportionally.

In the U.S., diabetes fueled a marked increase in the prevalence of kidney failure over the last 30 years and now accounts for half of all new cases of kidney failure.
Moreover, CKD markedly amplifies risks of **ASCVD**, **heart failure** (HF), **cardiovascular death**, and **all-cause mortality** among people with diabetes.
In the U.S., one of every five adults with diabetes is not aware of their diagnosis.
Awareness of CKD is even lower with 9 of 10 individuals unaware of having underlying CKD, including 2 of 5 with severe CKD.
In addition, both diabetes and CKD *disproportionately* affect racial and ethnic minorities and older adults.
Insufficient screening, diagnosis, and awareness impair efforts to implement treatment and improve outcomes and exacerbate racial, socioeconomic, and ethnic disparities.

In the U.S., the total estimated cost of diagnosed diabetes in 2017 was $327 billion, including $237 billion in direct medical costs and $90 billion in reduced productivity. The estimated global direct health expenditure on diabetes in 2019 was $760 billion.

CKD, with and without kidney failure, is a major driver of the cost of diabetes care. Costs of CKD, stroke, and heart disease are additive.

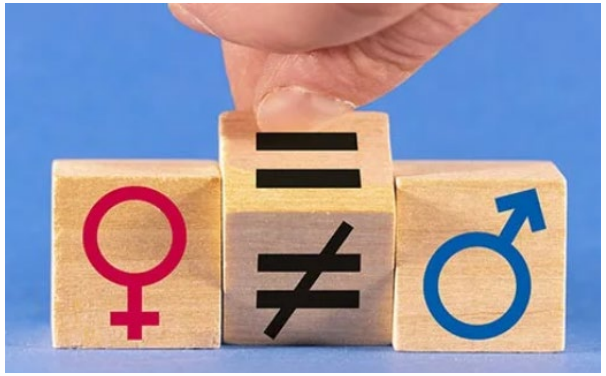
Gli studi dimostrano che la coesistenza di DM e MRC si associa ad un ***tasso di mortalità*** significativamente più elevato rispetto a quello delle due condizioni valutate separatamente.

L'incidenza di ESRD nel soggetto diabetico è rimasta pressoché invariata negli ultimi 20 anni (con un'incidenza di uremia terminale ed inizio di trattamento renale sostitutivo che varia dallo **0,04% all' 1,8% per anno**) , mentre si è assistito ad una significativa riduzione di altre complicanze cardiovascolari, quali l'infarto miocardico acuto, l'ictus cerebri e le amputazioni.

L'insuccesso nel miglioramento della prognosi renale del DM può avere ragioni diverse.:

- l'aumento dell'età anagrafica media, la migliorata assistenza e cura del paziente diabetico (per esempio in caso di infarto miocardico acuto),
- l'avvento di importanti classi farmacologiche (ad es. β-bloccanti, ACE-I, sartani, etc.,) implicano che la popolazione diabetica è sempre più anziana, fragile e con pluripatologie;
- lo stretto controllo glicemico ha un ruolo chiave nel ridurre il rischio di insorgenza e/o la progressione del danno renale, in assenza, fino a qualche anno addietro, di ipoglicemizzanti ad ***attività nefroprotettiva diretta***

Diabetologia e Medicina di Genere: un gruppo di studio per una maggiore equità di trattamento



Nel capitolo del libro «**La Medicina di Genere: Importanza e Normative**”, a firma del **professor Luzi**, in collaborazione con la prof.ssa **Daniela Perani** dell’Università Vita-Salute San Raffaele che ha evidenziato le caratteristiche genere-specifiche delle interazioni metabolismo-cervello, viene affrontata la cosiddetta **Sindrome di Yentl in campo diabetologico**. Questa condizione – che consiste in una **minore attenzione diagnostica verso le donne in condizioni di cardiopatia** – viene presentata sottolineando le **disparità di genere nel trattamento del diabete**, attraverso la disamina dei più recenti studi scientifici sul tema. Nell’ambito di una collaborazione tra Istituti di Ricovero e Cura a Carattere Scientifico (IRCCS), inoltre, il professor Luzi sta proseguendo il lavoro di ricerca per identificare **differenze cerebrali genere-specifiche** nell’**obesità** e nel **diabete**.

3 novembre 2022

Storia naturale della nefropatia diabetica

Evoluzione della nefropatia	Progressi-one temporale	Filtrato glomerulare e flusso plasmatico renale	Esame urine	Esame del sangue	Situazione clinica	Alterazioni morfologiche
I Iperfunzione	Alla diagnosi di diabete	Aumentati	Nella norma	Nella norma	Volume renale aumentato	Ipertrofia glomerulare
II Latenza clinica	2-5 anni	Normali-aumentati	Microalbuminuria reversibile	Nella norma	Nella norma	Ispessimento membrana basale
III Nefropatia incipiente	5-15 anni	Normali-aumentati	Microalbuminuria	Nella norma	Aumento pressione arteriosa	Ulteriore espansione mesangiale
IV Nefropatia clinicamente manifesta	10-25 anni	Ridotti ed in riduzione	Proteinuria persistente (>0.5g/24h)	Lento aumento della creatinina	Ipertensione nel 60-70% dei pazienti	Glomerulosclerosi nodulare diffusa
V Insuffcienza renale	15-30 anni	Ridotti ed in riduzione	Proteinuria persistente	Creatinina sopra i valori di norma	Ipertensione nel 90-100% dei pazienti	Progressione della sclerosi, occlusione dei capillari

Mogensen CE et al. *Lancet* 346: 1080-1084,

Il rene riveste un ruolo importante nel mantenimento dell'omeostasi del glucosio.

È sede di *gluconeogenesi*, sebbene in misura nettamente inferiore rispetto al fegato, ma soprattutto è impegnato nel *riassorbimento del glucosio* che filtra liberamente a livello glomerulare.

Il glucosio, essendo un composto polare, per attraversare la membrana plasmatica necessita di proteine di trasporto.
Il passaggio del glucosio dal lume del tubulo all'interno della cellula avviene per trasporto attivo mediato da due *cotrasportatori sodio/glucosio*, **SGLT2 e SGLT1:**
- Il primo è localizzato nel *segmento S1 del tubulo prossimale* ed è responsabile del riassorbimento di circa il 90% del glucosio filtrato;
- il secondo si trova più a valle, nel *segmento S3 del tubulo prossimale*, oltreché a *livello intestinale*, ed è deputato al riassorbimento della restante parte.
Il glucosio filtrato viene totalmente riassorbito nel tubulo, fino ad un valore soglia di saturazione del sistema, corrispondente ad una glicemia di 180-200 mg/dL

Studi sperimentali suggeriscono che l'aumento del glucosio filtrato è il primum movens dell'***iperfiltrazione glomerulare***.

Il legame tra carico di glucosio e incremento del filtrato glomerulare renale (GFR) è rappresentato dal *tubulo renale prossimale* (ipotesi tubulare).

Il glucosio agisce sulle cellule tubulari sia direttamente che indirettamente attraverso *l'angiotensina II*, di cui determina un'aumentata produzione intrarenale: attiva multiple vie di trasduzione intracellulare del segnale che conducono all'aumentata sintesi di fattori quali il VEGF. Il tubulo va incontro inizialmente ad ***iperplasia*** e successivamente ad ***ipertrofia*** *(*aumento volumetrico del rene). Inoltre, di grande importanza, si realizza un'***iperespressione degli SGLT.***

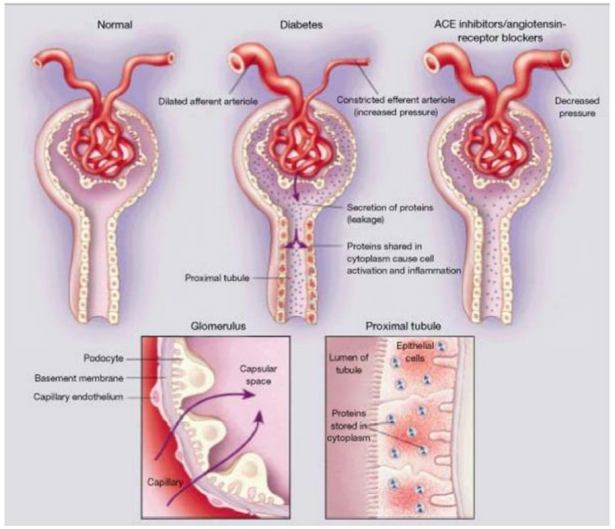
Trattandosi di un sistema di cotrasporto del tipo simporto, non solo il glucosio ma anche il ***sodio*** va incontro ad aumentato riassorbimento: una ridotta quantità ne giunge alla macula densa con *soppressione del feedback tubulo-glomerulare*, un meccanismo di autoregolazione del flusso ematico renale e del GFR di norma costantemente attivo. Si realizza una condizione di *vasodilatazione dell'arteriola afferente, ipertensione ed iperfiltrazione glomerulare.*

L'aumentato riassorbimento di glucosio favorisce la persistenza di iperglicemia, che è causa di tossicità tubulare per aumentato consumo di energia e ossigeno: si determina *danno ipossico, produzione di radicali liberi dell'ossigeno e stress ossidativo, flogosi e fibrosi tubulo-interstiziale*.

L'iperfiltrazione glomerulare è un'alterazione dell'emodinamica renale che si osserva nelle fasi iniziali della MRC nel 40% dei diabetici di tipo 2 e nel 75 % dei diabetici di tipo 1.

GIN 2020 G. Costanza et al

DIABETE e RENE: FISIOPATOLOGIA



La storia naturale della nefropatia diabetica muove dall'**ipertensione glomerulare**, causa di *ispessimento della membrana basale glomerulare ed espansione del mesangio,* per accumulo di matrice extracellulare.

La progressiva espansione del mesangio può portare alla formazione di noduli di matrice con cellule mesangiali disposte a palizzata perifericamente (***noduli di Kimmelstiel-Wilson***), che possono comprimere i capillari e generare microaneurismi.

A livello vascolare si osserva anche ***arteriosclerosi ialina***.

Nella componente **endoteliale** si rileva *fusione dei pedicelli* e progressiva ***riduzione del numero dei podociti***. Sul piano clinico è descritta la comparsa di *microalbuminuria* prima e *macroalbuminuria* dopo, in presenza di GFR normale o aumentato.

GIN 2020 G. Costanza et al

DIABETE e RENE: FISIOPATOLOGIA

Successivamente al danno glomerulare si aggiungono le alterazioni tubulo-interstiziali da *tossicità tubulare da glucosio e proteine*. Si osserva ***atrofia tubulare*** ed ***espansione interstiziale***, inizialmente dovuta soprattutto ad aumento della componente cellulare, con evoluzione verso la ***sclerosi globale e segmentale e declino del GFR.***

L'iperfiltrazione glomerulare non sempre rappresenta il meccanismo fisiopatologico primario e più importante nell'instaurarsi del danno renale.

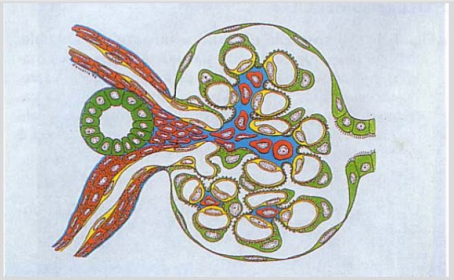
GIN 2020 G. Costanza et al

E la PROTEINURIA????

Lo studio UKPDS ha rivelato che una percentuale significativa di soggetti affetti da DM2 presentava un declino della funzione renale prima o senza che *mai si evidenziasse proteinuria patologica*. Il raddoppio della creatinina o la riduzione del GFR sotto la soglia di 60 mL/min/1.73m2 sono stati registrati nel 30% della popolazione diabetica, in un tempo mediano di 15 anni dalla diagnosi. Ebbene, *solo nel 40% di questi soggetti il peggioramento della funzione renale era preceduto dall'evidenza di proteinuria e nella stessa percentuale la proteinuria non veniva documentata mai*.

Ulteriori evidenze indicano che i casi di ***nefropatia diabetica in assenza di proteinuria patologica*** sono in progressivo aumento: dal confronto tra i periodi 1988-1994 e 2009-2014 è emerso che negli USA la prevalenza del fenotipo albuminurico si è ridotta dal 21 al 16 % .

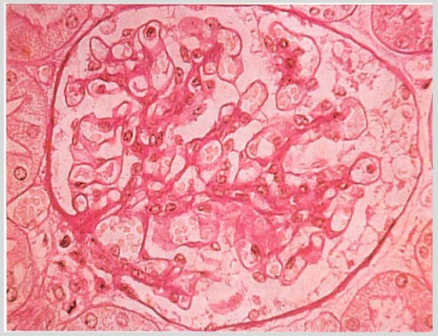
È stato ipotizzato che questo trend possa trovare spiegazione negli interventi di ***prevenzione primaria e secondaria*** posti in essere negli ultimi decenni al fine di prevenire e trattare tempestivamente le complicanze cardiovascolari e renali del diabete, quale l'impiego dei bloccanti del RAS.

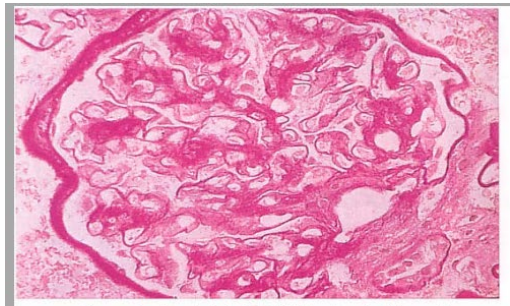


Rappresentazione schematica del Glomerulo e strutture adiacenti:

Cellule epiteliali (-podociti-cell. Parietali della capsula Bowman-cell. Tub. Distale)
Cellule endoteliali
Membrane basali
Matrice mesangiale.
Cellule mesangiali -cellule apparato iuxtaglomerulare (dentro il triangolo formato da arteriola afferente, efferente e tubulo distale)
Cellule muscolari liscie delle arteriole

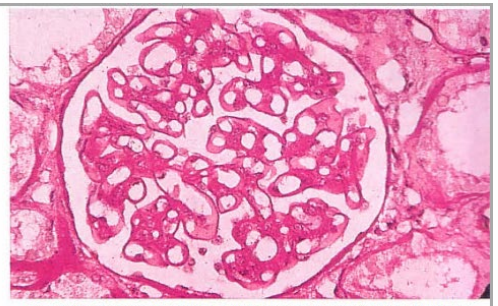
Sezione ilare di un glomerulo normale. Colorazione PAS x260





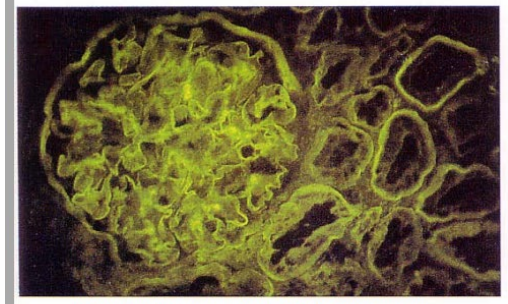
Glomerulosclerosi diabetica iniziale sclerosi diffusa e lieve ispessimento mesangio e della capsula di Bowman x390

14-1



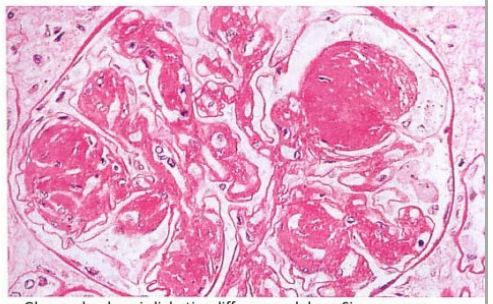
Fase più avanzata. Mesangio più prominente e MB dei capillari più ispessite. x390

14-2



Immunofluorescenza. Glomerulosclerosi diffusa con Depositi IgG lungo MB dei capillari e dei tubuli x260

14-3



Glomerulosclerosi diabetica diffusa e nodulare. Si osserva un nodulo ben formato alle ore 15 e uno meno compatto ore 8 x260

14-4

LESIONI ANATOMO-PATOLOGICHE (nefropatia diabetica)

- **ISPESSIMENTO MEMBRANA BASALE** (glomerulare, tubulare e della capsula di Bowman).
- **IALINOSI DELLE ARTERIE GLOMERULARI** (Lesioni capsulari **"Cappelli fibrinoidi"** nelle pareti capillari a livello subendoteliale; **"Gocce Capsulari"** tra la MB della capsula del Bowman e le cellule epiteliali parietali.
- **ESPANSIONE MESANGIALE** (della matrice per i 2/3 e delle cell. mesangiali per 1/3)
- di tipo DIFFUSO (80%) e NODULARE di (Kimmestiel – Wilson) (20%).
- **FIBROSI TUBULO-INTERSTIZIALE**
- **DEPOSITI LINEARI DI IgG** nella Membrana Basale (glomerulo e tubuli)

DIABETE e RENE: FISIOPATOLOGIA

Il danno renale correlato al DM2 include :

- Alterazioni di carattere strutturale (*ispessimento della membrana basale glomerulare, espansione mesangiale, fibrosi interstiziale, perdita dell'architettura capillare, ialinosi delle arterie di piccolo e medio calibro*):
- Alterazioni di carattere funzionale (*disfunzione della catena respiratoria mitocondriale, over espressione di citochine pro-infiammatorie quali IL-6, IL-8, IL-18, TNF-α, INF-γ*) indotte dall'iperglicemia.

Le manifestazioni cliniche che ne conseguono configurano la cosiddetta "***malattia renale in corso di diabete***" (diabetic kidney disease, DKD), caratterizzata da ***proteinuria selettiva e non selettiva, ipertensione arteriosa e declino progressivo della funzionalità renale***.

GIN 2021, A. Granata et al.

Le strategie terapeutiche attuali mirano ad ottimizzare il controllo glicemico attraverso varie modalità:

a) incrementando la disponibilità di insulina circolante, mediante la somministrazione di insulina esogena oppure mediante farmaci che promuovono la secrezione di insulina endogena;
b) migliorando la sensibilità insulinica dei tessuti;
c) ritardando l'assorbimento dei carboidrati a livello intestinale;
d) promuovendo l'escrezione urinaria di glucosio.

La presenza di malattia renale cronica (CKD) è in grado di ***condizionare la farmacocinetica e la farmacodinamica di diverse molecole***. In merito alle opzioni terapeutiche per il trattamento del diabete mellito di tipo 2, bisogna considerare tre ordini di problemi:

- il fatto che i farmaci impiegati per il trattamento del diabete mellito risentono dell'eventuale presenza di malattia renale;
- il fatto che tali terapie possono necessitare di modifiche ed impattare sull' outcome "renale";
- i profili di sicurezza dei suddetti farmaci mutano man mano che si assiste al declino della funzione renale.

OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

SUPPLEMENT TO

kidney INTERNATIONAL

KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease

VOLUME 98 | ISSUE 4S | OCTOBER 2020

www.kidney-international.org

Top 10 Takeaways for Clinicians from the KDIGO 2020 Clinical Practice Guideline for Diabetes Management in CKD[1]

1 Comprehensive care
Patients with diabetes and CKD have multisystem disease that requires treatment including a foundation of lifestyle intervention (healthy diet, exercise, no smoking) and pharmacologic risk factor management (glucose, lipids, blood pressure).

2 Nutrition intake
Patients should consume a balanced, healthy diet that is high in vegetables, fruits, whole grains, fiber, legumes, plant-based proteins, unsaturated fats, and nuts; and lower in processed meats, refined carbohydrates, and sweetened beverages. Sodium (<2 g/day) and protein intake (0.8 g/kg/day) in accordance with recommendations for the general population.

3 Glycemic monitoring
It is advised to monitor glycemic control with HbA1c in patients with diabetes and CKD. For patients with advanced CKD (particularly those on dialysis), reliability of HbA1c decreases and results should be interpreted with caution. CGM or SMBG may also be useful, especially for treatment associated with risk of hypoglycemia.

4 Glycemic targets
Targets for glycemic control should be individualized ranging from <6.5% to <8.0%, taking into consideration risk factors for hypoglycemia, including advanced CKD and type of glucose-lowering therapy.

5 SGLT2i
SGLT2i should be initiated for patients with T2D and CKD when eGFR is ≥30 ml/min/1.73 m² and can be continued after initiation at lower levels of eGFR. SGLT2i markedly reduce risks of CKD progression, heart failure, and atherosclerotic cardiovascular diseases, even when blood glucose is already controlled.

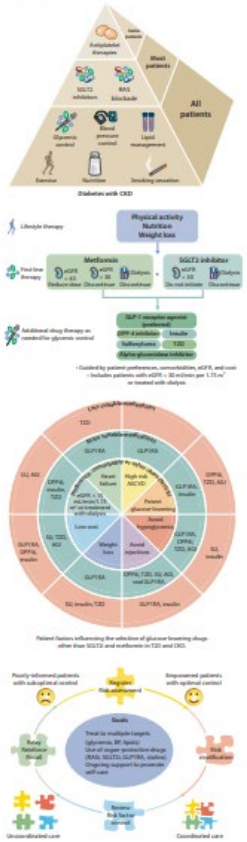
6 Metformin
Metformin should be used for patients with T2D and CKD when eGFR is ≥30 ml/min/1.73 m². For such patients, metformin is a safe, effective, and inexpensive drug to control blood glucose and reduce diabetes complications.

7 GLP-1 RA
In patients with T2D and CKD who have not achieved individualized glycemic targets despite use of metformin and SGLT2i, or who are unable to use those medications, a long-acting GLP-1 RA is recommended as part of the treatment.

8 RAS blockade
Patients with T1D or T2D, hypertension, and albuminuria (persistent ACR >30 mg/g) should be treated with a RAS inhibitor (ACEi or ARB), titrated to the maximum approved or highest tolerated dose. Serum potassium and creatinine should be monitored.

9 Approaches to management
A team-based and integrated approach to manage these patients should focus on regular assessment, control of multiple risk factors, and structured education in self-management to protect kidney function and reduce risk of complications.

10 Research recommendations
There is a paucity of data on optimal management of diabetes in kidney failure, including dialysis and transplantation, which should be a focus for future studies.



ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-creatinine ratio; AGI, alpha-glucosidase inhibitor; ARB, angiotensin II receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CKD, chronic kidney disease; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c (glycated hemoglobin); RAS, renin-angiotensin system; RASi, renin-angiotensin system inhibitor; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SMBG, self-monitoring blood glucose; SU, sulfonylurea; T1D, type 1 diabetes; T2D, type 2 diabetes; TZD, thiazolidinedione

Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2020;98(4S):S1-S115. Available at: https://kdigo.org/guidelines/diabetes-ckd/

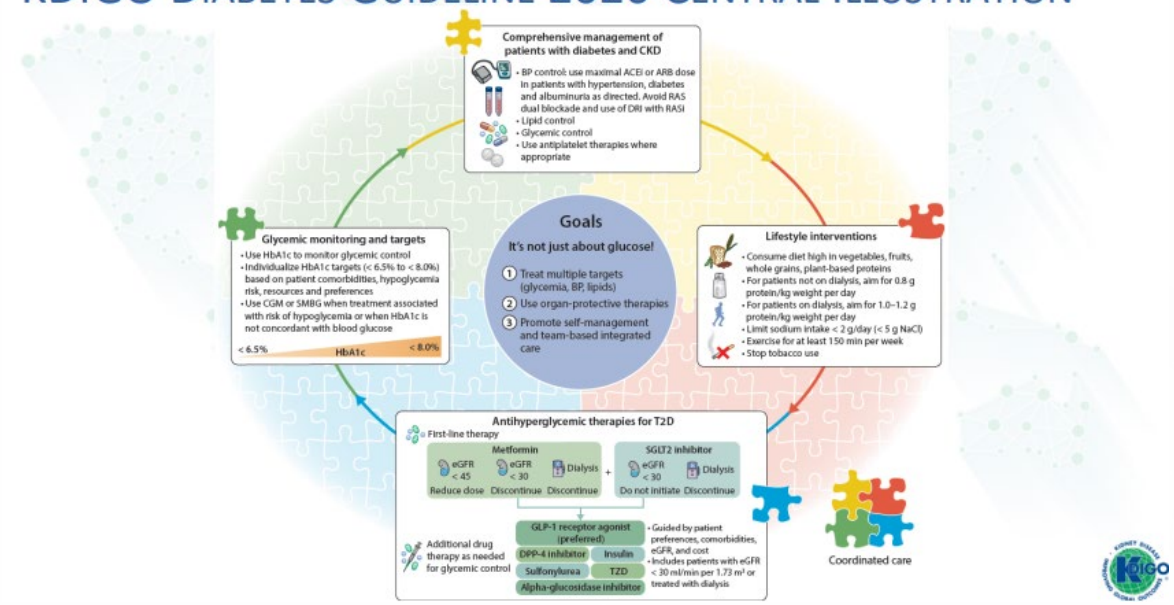
Executive summary of the 2020 KDIGO Diabetes Management in CKD Guideline: evidence-based advances in monitoring and treatment

Check for updates

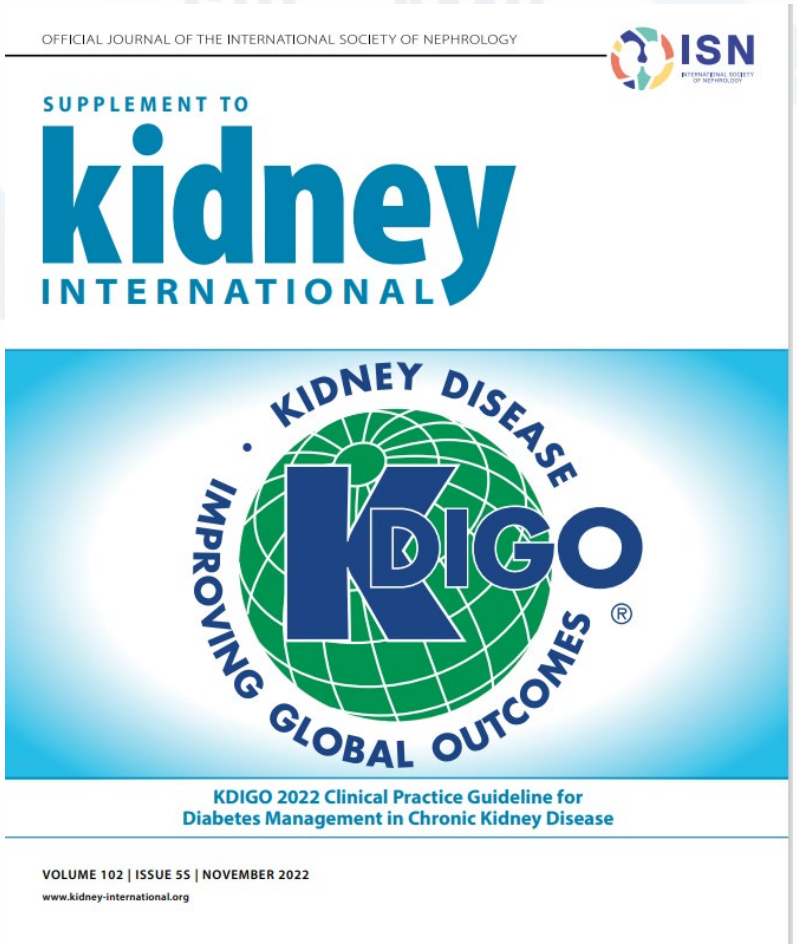
OPEN

Ian H. de Boer[1], M. Luiza Caramori[2], Juliana C.N. Chan[3], Hiddo J.L. Heerspink[4], Clint Hurst[5], Kamlesh Khunti[6], Adrian Liew[7], Erin D. Michos[8], Sankar D. Navaneethan[9], Wasiu A. Olowu[10], Tami Sadusky[11], Nikhil Tandon[12], Katherine R. Tuttle[13], Christoph Wanner[14], Katy G. Wilkens[15], Sophia Zoungas[16], Lyubov Lytvyn[17], Jonathan C. Craig[18,19], David J. Tunnicliffe[19,20], Martin Howell[19,20], Marcello Tonelli[21], Michael Cheung[22], Amy Earley[22] and Peter Rossing[23]

KDIGO Diabetes Guideline 2020 Central Illustration



	ADA 2020	ESC/EASD 2019	KDIGO 2020
ACEi/ ARBs	Strongly recommended in patients with **hypertension** and **UACR ≥300 mg/g** and/or **eGFR <60ml/min/1.73 m²** Recommended in patients with **hypertension** and **UACR 30–299 mg/g**	Recommended for treatment of **hypertension**, particularly in presence of **UACR ≥30 mg/g**, proteinuria or left ventricular hypertrophy	Recommended in patients with **diabetes**, **hypertension** and **albuminuria**
SGLT-2i	Consider in patients with an **eGFR ≥30 ml/min/1.73 m²** and **UACR >30 mg/g**, particularly those with **UACR >300 mg/g**, to reduce risk of CKD progression, CV events, or both	Recommended if **eGFR is 30–<90 ml/min/1.73 m²** (associated with lower risk of renal endpoints)	Recommended in **combination with metformin** in patients with **T2D**, **CKD** and an **eGFR ≥30 ml/min/1.73 m²**
GLP-1 RA	May reduce risk of progression of albuminuria, CV events, or both in patients with **CKD and increased CV risk**	Suggested if **eGFR >30 ml/min/1.73 m²** (liraglutide and semaglutide associated with lower risk of renal endpoints)	A **long-acting GLP-1RA** is recommended in patients with T2D and CKD who have **not achieved individual glycaemic targets despite use of metformin/SGLT-2i**



The update was motivated by the wealth of high-quality new evidence that has quickly become available since the original 2020 guideline was published and calls from the community to help guide application of these new data.

The short interval between guidelines reflects the rapid pace of advances in the management of diabetes and CKD. The scope of the **2022 guideline** is unchanged from 2020. The guideline addresses both type 1 diabetes (T1D) and type 2 diabetes (T2D), all stages of CKD, patients with a kidney transplant, and patients treated with hemodialysis or peritoneal dialysis.

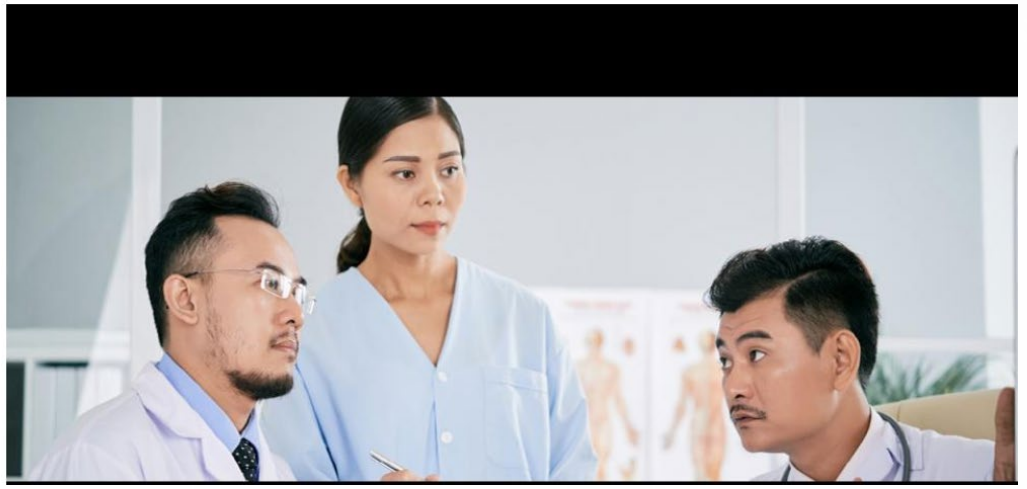
Lifestyle, pharmacologic, self-care, and systems interventions were all evaluated.

The guideline focuses on clinical management questions that can be addressed with high-quality scientific evidence, specifically, randomized controlled trials (RCTs) that evaluated clinically relevant outcomes.

Patients know themselves better than anyone else, and although health care professionals have the medical background, when a *patient and health care professional become partners in developing a shared-decision treatment plan* the lives of the patients will improve.
Patient priorities often do not align with healthcare professional priorities. Ideally, health care professionals will question patients about their priorities and together they will establish an agreed upon care program.

The American Diabetes Association and Kidney Disease: Improving Global Outcomes Release a Joint Consensus Report on Diabetes Management in Chronic Kidney Disease

October 04, 2022 | Arlington, Virginia



Both the ADA and KDIGO guidelines emphasize the importance of a ***team-based integrated approach*** that engages diabetes care and education specialists, physicians, nurse practitioners, physician assistants, nurses, dietitians, exercise specialists, pharmacists, dentists, podiatrists, and/or mental health professionals in the care of the patient, with multidisciplinary care models representing a key strategy to overcome barriers o effective management of patients with diabetes and CKD.

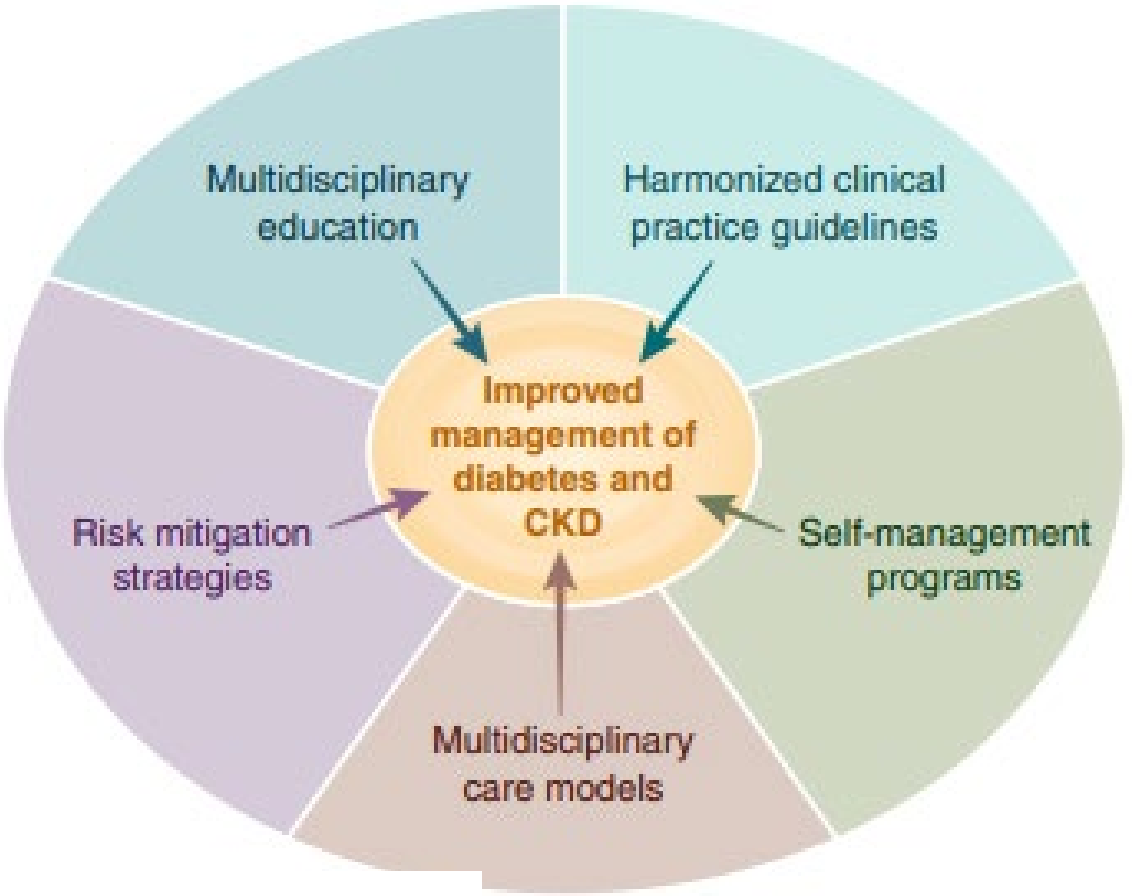


Figure 4—Overcoming barriers to management of CKD in patients with diabetes. Barriers such as low CKD awareness, high complexity of care, difficulties with adhering to increasingly complex treatment regimens, and low recognition and application of guideline-directed management all contribute to suboptimal management of patients with diabetes and CKD. Proposed strategies that may contribute to improved management of patients with diabetes and CKD include implementation of multidisciplinary models of care, structured risk mitigation strategies and education, multidisciplinary educational initiatives, harmonization of clinical practice guidelines, and provision of self-management programs for patients with diabetes and CKD.

Executive summary of the KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease: an update based on rapidly emerging new evidence

Peter Rossing[1,2], M. Luiza Caramori[3], Juliana C.N. Chan[4,5], Hiddo J.L. Heerspink[6], Clint Hurst[7], Kamlesh Khunti[8], Adrian Liew[9], Erin D. Michos[10], Sankar D. Navaneethan[11,12], Wasiu A. Olowu[13], Tami Sadusky[14], Nikhil Tandon[15], Katherine R. Tuttle[16], Christoph Wanner[17], Katy G. Wilkens[18], Sophia Zoungas[19], Jonathan C. Craig[20,21], David J. Tunnicliffe[21,22], Marcello A. Tonelli[23], Michael Cheung[24], Amy Earley[24] and Ian H. de Boer[25]

Based on this updated review, Chapters 1 (*Comprehensive care*) and 4 (*Glucose-lowering therapies*) were substantially revised. These include full revisions for the use of sodiumglucose co-transporter-2 inhibitors (SGLT2i) and glucagonlike peptide-1 receptor agonists (GLP-1 RA), and the development of a new section on mineralocorticoid receptor antagonists (MRA).

Chapters 2 (*Glycemic monitoring and targets in patients with diabetes and CKD*), 3 (*Lifestyle interventions in patients with diabetes and CKD*), and 5 (*Approaches to management of patients with diabetes and CKD*) were deemed current, and no changes were made to recommendations or practice points.

Top 10 Takeaways for Clinicians from the KDIGO 2022 Clinical Practice Guideline for Diabetes Management in CKD

1 Comprehensive care
Patients with diabetes and CKD have multisystem disease that requires treatment including a foundation of lifestyle intervention (healthy diet, exercise, weight management, no smoking) and drug therapy that improves kidney and cardiovascular outcomes (glucose, lipids, blood pressure).

2 Nutrition intake
Patients should consume a balanced, healthy diet that is high in vegetables, fruits, whole grains, fiber, legumes, plant-based proteins, unsaturated fats, and nuts; and lower in processed meats, refined carbohydrates, and sweetened beverages. Sodium (<2 g/day) and protein intake (0.8 g/kg/day) in accordance with recommendations for the general population.

3 SGLT2i
SGLT2i should be initiated for patients with T2D and CKD when eGFR is ≥20 ml/min/1.73 m^2 and can be continued after initiation at lower levels of eGFR. SGLT2i markedly reduce risks of CKD progression, heart failure, and atherosclerotic cardiovascular diseases, even when blood glucose is already controlled.

4 Metformin
Metformin should be used for patients with T2D and CKD when eGFR is ≥30 ml/min/1.73 m^2. For such patients, metformin is a safe, effective, and inexpensive drug to control blood glucose and reduce diabetes complications.

5 Glycemic monitoring and targets
HbA1c should be measured regularly. Reliability decreases with advanced CKD, particularly for patients treated with dialysis, and results should be interpreted with caution. CGM or SMBG may also be useful, especially for treatment associated with risk of hypoglycemia. Targets for glycemic control should be individualized, ranging from <6.5% to <8.0%.

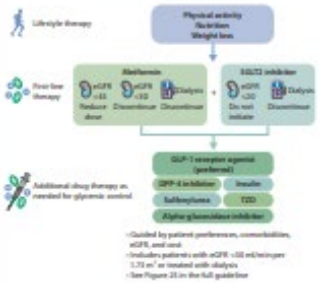
6 GLP-1 RA
In patients with T2D and CKD who have not achieved individualized glycemic targets despite use of metformin and SGLT2i, or who are unable to use those medications, a long-acting GLP-1 RA is recommended as part of the treatment.

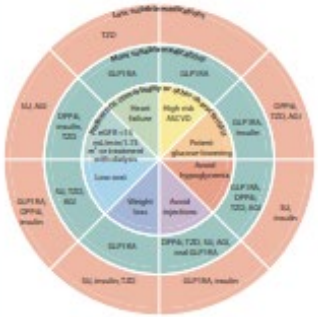
7 RAS blockade
Patients with T1D or T2D, hypertension, and albuminuria (persistent ACR ≥30 mg/g) should be treated with a RAS inhibitor (ACEi or ARB), titrated to the maximum approved or highest tolerated dose. Serum potassium and creatinine should be monitored.

8 Non-steroidal mineralocorticoid antagonists (ns-MRA)
ns-MRA reduce risks of CKD progression and cardiovascular events for people with T2D and residual albuminuria. They are suggested for patients with T2D, urine ACR ≥30 mg/g, and normal serum potassium on other standard of care therapies. Serum potassium and creatinine should be monitored.

9 Approaches to management
A team-based and integrated approach to manage these patients should focus on regular assessment, control of multiple risk factors, and structured education in self-management to protect kidney function and reduce risk of complications.

10 Research recommendations
There is a paucity of data on optimal management of diabetes in kidney failure, including dialysis and transplantation, which should be one important focus for future studies.





ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-creatinine ratio; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c (glycated hemoglobin); RAS, renin-angiotensin system; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SMBG, self-monitoring blood glucose; T1D, type 1 diabetes; T2D, type 2 diabetes

Top 10 Takeaways for Patients from the KDIGO 2022 Clinical Practice Guideline for Diabetes Management in CKD

1 Comprehensive care
Combining a healthy diet, exercise, smoking cessation, and management of glucose, blood pressure, and lipids with appropriate medications can reduce risks of kidney failure, heart attack, stroke, and heart failure.

2 Nutrition intake
Consume a balanced, healthy diet: higher in vegetables, fruits, whole grains, fiber, legumes, plant-based proteins, unsaturated fats, and nuts; and lower in processed meats, simple carbohydrates like sugars or white flours, and sweetened beverages. Salt intake should be less than 5 grams per day (equivalent to 2 grams of sodium) and protein should be maintained at 0.8 grams of protein per kilogram of weight per day. These levels should be reviewed by a dietician, and monitored on a regular basis.

3 SGLT2i
SGLT2i (sodium-glucose cotransporter-2 inhibitor) medications were developed to lower blood sugar, but in addition they reduce the risk of kidney failure and cardiovascular disease while lowering blood sugar. They can be started for people with type 2 diabetes and eGFR ≥20 ml/min/1.73 m^2.

4 Metformin
Metformin should also be given as an initial therapy to lower blood sugar. It can only be used for people with type 2 diabetes and kidney disease stages 1–3 (eGFR ≥30 ml/min/1.73 m^2).

5 Glycemic monitoring and targets
HbA1c should be measured regularly in patients with diabetes and CKD. HbA1c reliability decreases for patients with advanced CKD, particularly for those on dialysis, and results should be interpreted with caution. CGM or SMBG may also be useful, especially for treatment associated with risk of hypoglycemia. Targets for glycemic control should be individualized, ranging from <6.5% to <8.0%, taking into consideration risk factors for hypoglycemia, including advanced CKD and type of glucose-lowering therapy.

6 GLP-1 RA
If you have type 2 diabetes and have not met your target blood sugar with the use of metformin and SGLT2i or are not able to take these medications, your clinician may prescribe a long-acting GLP-1 RA (glucagon-like peptide-1 receptor agonist) which is a blood sugar-lowering medication with added benefit to the heart.

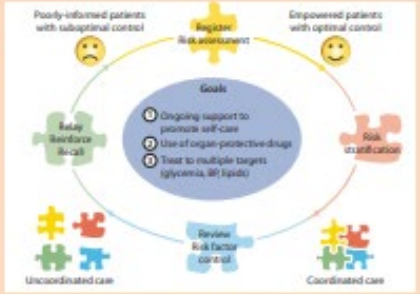
7 RAS blockade
An ACE (angiotensin-converting enzyme) inhibitor or ARB (angiotensin II receptor blocker) – both blood pressure-lowering medications with kidney protective effects – should be given if you have diabetes (type 1 or type 2), high blood pressure, and protein in your urine, sometimes called albuminuria. Kidney function and levels of potassium in your blood should be monitored.

8 Non-steroidal mineralocorticoid antagonists (ns-MRA)
ns-MRA reduce risks of CKD progression and cardiovascular events for people with T2D and residual albuminuria despite other treatments. They are suggested for patients with T2D, urine ACR ≥30 mg/g, and normal serum potassium on other standard of care therapies.

9 Approaches to management
Understanding your condition will be of great benefit. Be an active part of the team managing your diabetes and kidney disease. Focusing on self-management and control of multiple risk factors will help protect kidney function and reduce the risk of side effects from diabetes.

10 Become an empowered patient
Patients with diabetes feel overwhelmed with the lifestyle changes required of diabetes. Set small, daily goals to help manage what needs to be done.

Examples:
- Healthy eating – decrease dinner portion size;
- Exercise – walk 10 minutes extra each day;
- Health care team appointments – write down one question each week to ask about your care;
- Medicines – understand each medication you are required to take and why you are taking it;
- Side effects or complications – understand your risk factors, what are good lifestyle choices, and how these impact the side effects of diabetes.



SCREENING AND DIAGNOSIS

CKD is defined as persistent eGFR <60 mL/min/1.73 m2 , albuminuria (ACR >= 30 mg/g), or other markers of kidney damage, such as hematuria or structure abnormalities. Importantly, these measurements can vary within individuals over time, and persistence for at least 3 months is therefore required for diagnosis,

Both the ADA and KDIGO recommend *annual screening* of patients with diabetes for CKD.

Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO)

Ian H. de Boer,[1] Kamlesh Khunti,[2] Tami Sadusky,[3] Katherine R. Tuttle,[4] Joshua J. Neumiller,[5] Connie M. Rhee,[6] Sylvia E. Rosas,[7] Peter Rossing,[8,9] and George Bakris[10]

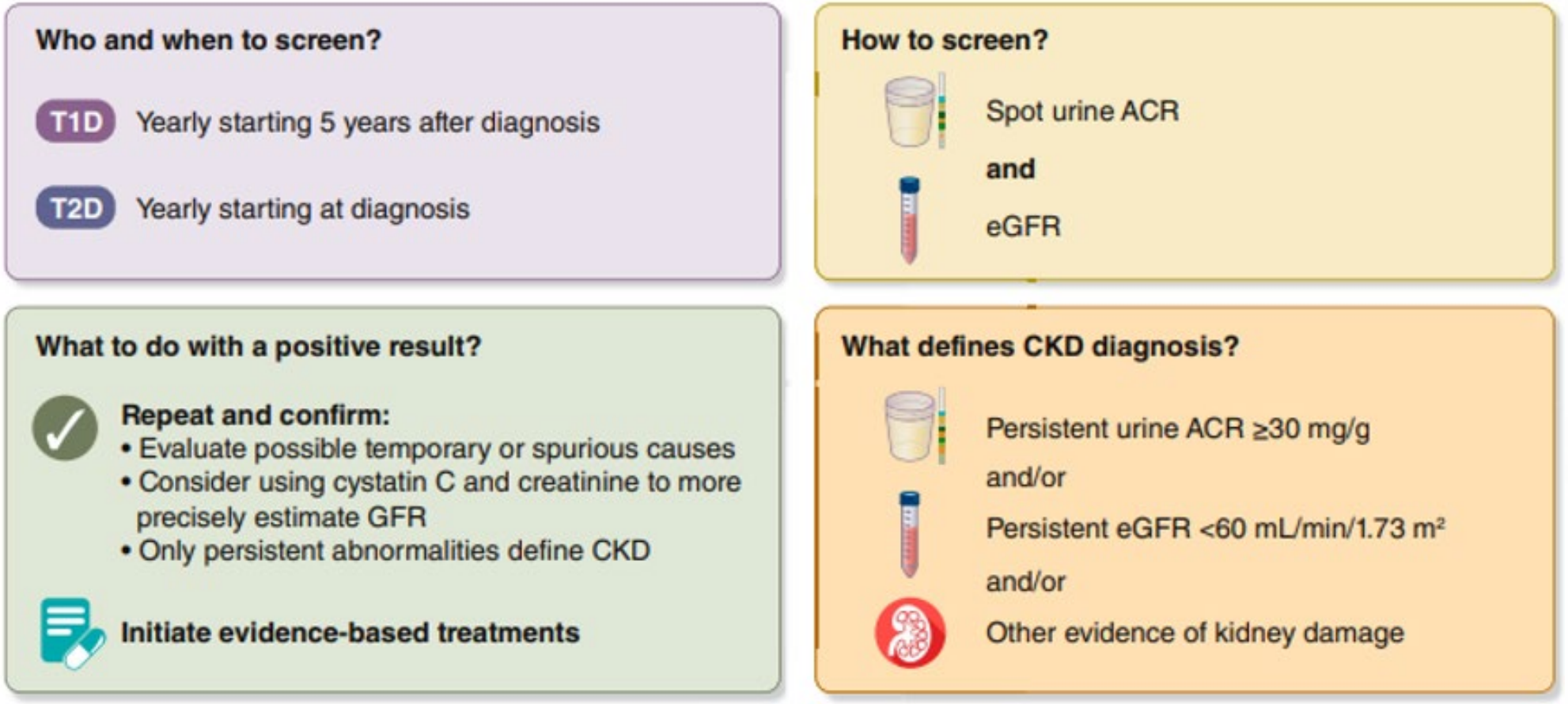


Figure 1—CKD screening and diagnosis for people living with diabetes. Screening includes measurement of both urine albumin and eGFR. Abnormalities should be confirmed. Persistent abnormalities in either urine ACR or eGFR (or both) diagnose CKD and should lead to immediate initiation of evidence-based treatments. ACR, albumin-to-creatinine ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; T1D, type 1 diabetes; T2D, type 2 diabetes.

Equazione	Cockcroft e Gault	MDRD	CKD-EPI
Vantaggi principali	• Facilmente calcolabile • Utilizzata dalla FDA per la stima della funzione renale e adattamento della dose di farmaci potenzialmente nefrotossici ***(scenario 1 e 2)***	• Per il calcolo non necessita del peso corporeo • Utilizzata da tutte le LG per classificare la MRC • Maggiore probabilità di identificare i veri malati in caso di potenziale danno renale (alta sensibilità) • Normalizzata per la BSA*, evita sovrastime in caso di obesità o sovraccarico volumetrico (ad es. scompenso)	• Stima della VFG più precisa grazie ai numerosi fattori di correzione • Più precisa in soggetti con funzione renale normale o lievemente ridotta
Limiti principali	• Per il calcolo necessita del peso corporeo • Non è normalizzata per la BSA* quindi rischia di **sovrastimare** la VFG negli obesi ***(scenario 3)*** • È meno accurata negli anziani (≥ 65 aa) e in presenza di danno renale grave (bassa sensibilità)	• Non è utilizzabile in soggetti con meno di 18 anni o più di 75 • Tende a **sottostimare** la VFG nei soggetti sani o con funzione renale lievemente ridotta quindi può generare "falsi malati" (bassa specificità per VFG 60-90 mL/min) ***(scenario 4)***	• Per il calcolo richiede formule matematiche complesse (vedi inserto)
		Entrambe le equazioni sono state validate con valori di Cr-s ottenuti con metodiche di laboratorio "standardizzate". Pertanto la stima risulta più attendibile quando si utilizzano valori di Cr-s ottenuti con sistemi standardizzati.[11]	

** BSA (Body Surface Area): superficie corporea (valore medio per l'adulto = 1.73 m^2)*

American Diabetes Association.
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KDIGO Kidney Disease Improving Global Outcomes

CKD is classified based on:
- **Cause (C)**
- **GFR (G)**
- **Albuminuria (A)**

GFR categories (mL/min/1.73 m²) Description and range				Albuminuria categories Description and range		
				A1	**A2**	**A3**
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–299 mg/g 3–29 mg/mmol	≥300 mg/g ≥30 mg/mmol
	G1	Normal or high	≥90	Screen 1	Treat 1	Treat and refer 3
	G2	Mildly decreased	60–89	Screen 1	Treat 1	Treat and refer 3
	G3a	Mildly to moderately decreased	45–59	Treat 1	Treat 2	Treat and refer 3
	G3b	Moderately to severely decreased	30–44	Treat 2	Treat and refer 3	Treat and refer 3
	G4	Severely decreased	15–29	Treat and refer* 3	Treat and refer* 3	Treat and refer 4+
	G5	Kidney failure	<15	Treat and refer 4+	Treat and refer 4+	Treat and refer 4+

Low risk (if no other markers of kidney disease, no CKD)
Moderately increased risk
High risk
Very high risk

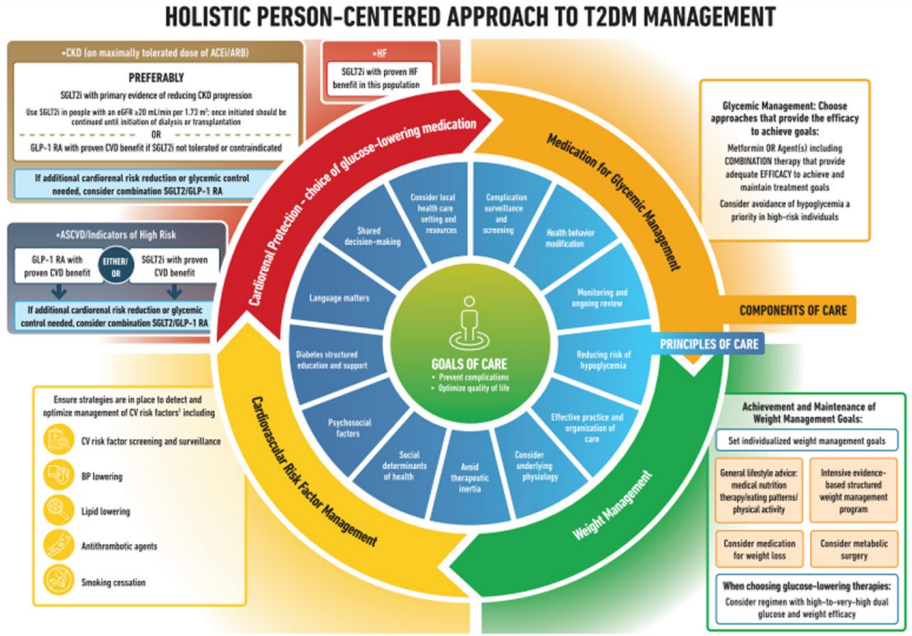
Figure 2—Risk of CKD progression, frequency of visits, and referral to nephrology according to GFR and albuminuria. The numbers in the boxes are a guide to the frequency of screening or monitoring (number of times per year). Green reflects no evidence of CKD by eGFR or albuminuria, with screening indicated once per year. For monitoring of prevalent CKD, suggested monitoring varies from once per year (yellow) to four times or more per year (i.e., every 1–3 months, [deep red]) according to risks of CKD progression and CKD complications. These are general parameters only, based on expert opinion, and underlying comorbid conditions and disease state must be taken into account, as well as the likelihood of impacting a change in management for any individual patient. CKD, chronic kidney disease; GFR, glomerular filtration rate.

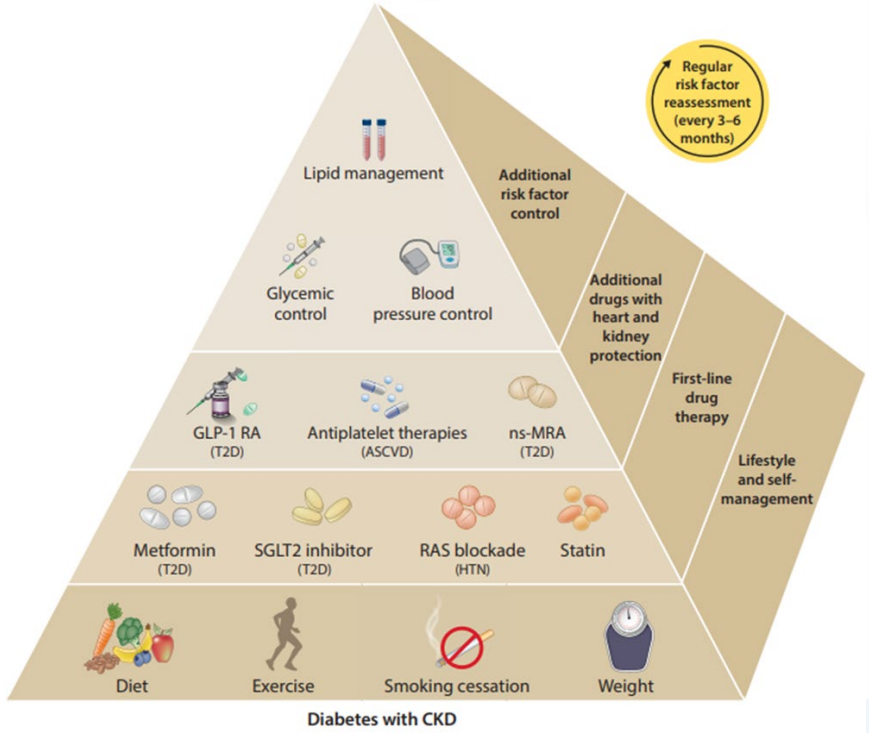
COMPREHENSIVE CARE

Multimorbidity is common in patients with diabetes and CKD, who are at high risk of *CKD progression, cardiovascular events, and premature mortality*. Therefore, both the ADA and KDIGO emphasize the importance of *comprehensive, holistic, patient-centered medical care* to improve overall patient outcomes.

The goals of comprehensive care are to treat the patient as a "whole" person and incorporate coordinated *multidisciplinary treatment, structured education to promote self-management, shared decision making, and primary and secondary prevention of diabetes-related complications, including CKD, ASCVD, and HF.*

This approach requires treatment directed *to optimize lifestyle, pharmacological therapy aimed at preserving organ function, and additional therapies aimed at improving intermediate risk factors such as glycemia, BP, and lipids.*

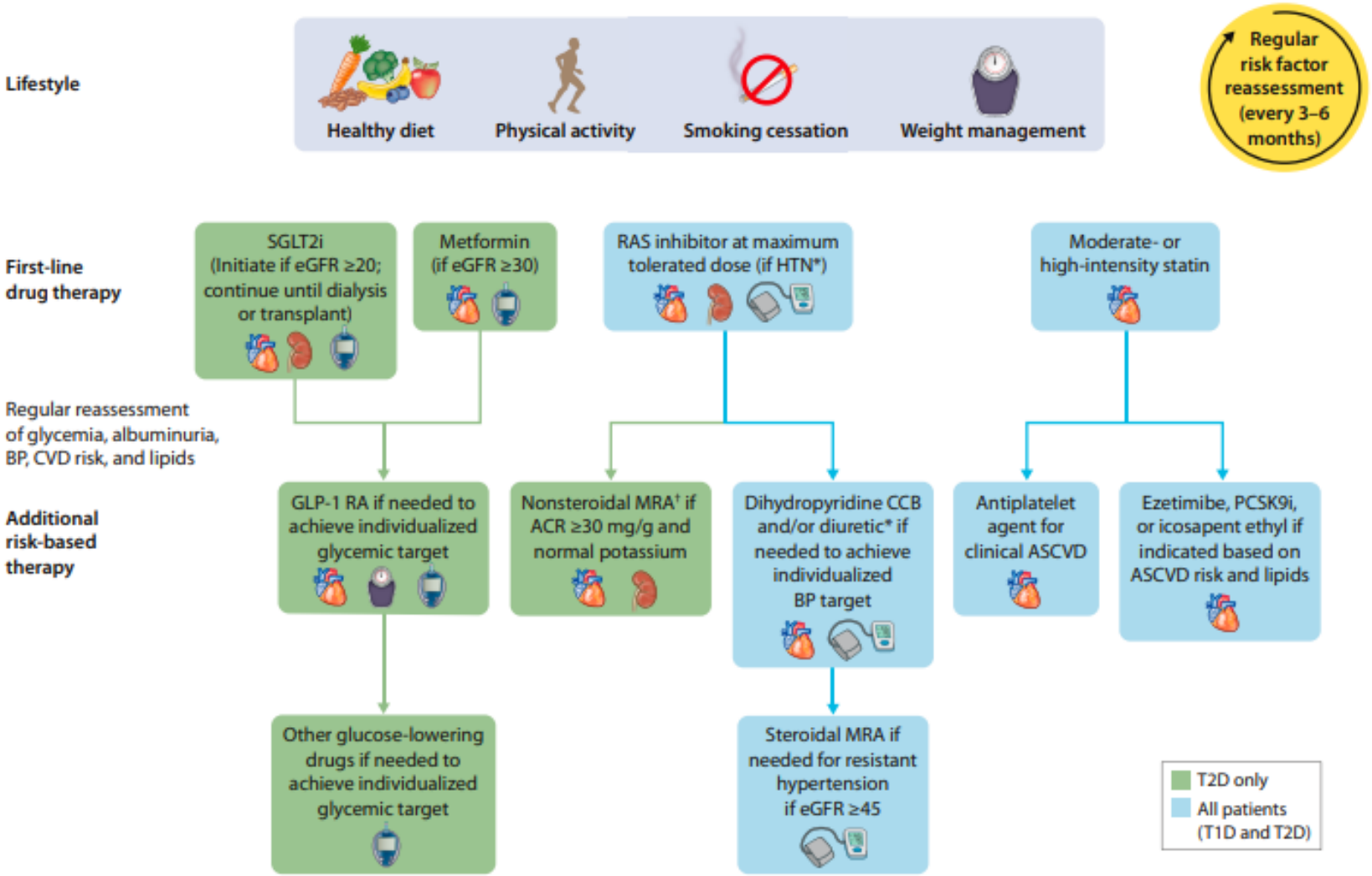




Chapter 1: Comprehensive care in patients with diabetes and CKD

1.1. Comprehensive diabetes and CKD management

Practice Point 1.1.1: Patients with diabetes and chronic kidney disease (CKD) should be treated with a comprehensive strategy to reduce risks of kidney disease progression and cardiovascular disease (Figures 1 and 2).



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KDIGO

Table 2—Considerations for selecting glucose-lowering agents in patients with T2D and CKD (2,17)

	Progression of CKD	ASCVD	Heart failure	Glucose-lowering efficacy	Hypoglycemia risk	Weight effects	Cost
Metformin	Neutral	Potential benefit	Potential benefit	High	Low	Neutral	Low
SGLT2 inhibitors	Benefit[a]	Benefit[c]	Benefit	Intermediate	Low	Loss	High
GLP-1 receptor agonists	Benefit[b]	Benefit[c]	Potential benefit	High	Low	Loss	High
DPP-4 inhibitors	Neutral	Neutral	Potential risk[c] (saxagliptin)	Intermediate	Low	Neutral	High
Insulin	Neutral	Neutral	Neutral	Highest	High	Gain	High (analogs) Low (human)
Sulfonylureas	Neutral	Neutral	Neutral	High	High	Gain	Low
Thiazolidinediones	Neutral	Potential benefit (pioglitazone)	Increased risk	High	Low	Gain	Low
α-Glucosidase inhibitors	Neutral	Neutral	Neutral	Intermediate	Low	Neutral	Low

Neutral

Potential benefit or intermediate glucose-lowering efficacy

Benefit (organ protection, high efficacy, low hypoglycemia risk, weight loss, or low cost)

Potential risk or high cost to patient

Increased risk for adverse effects

[a]Benefit supported by primary and secondary outcome data. [b]Benefit supported by secondary outcome data. [c]Benefit or risk is agent specific. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; SGLT2, sodium–glucose cotransporter 2.

Table 3—Key monitoring and risk mitigation strategies for preferred glucose-lowering agents

Medication	Consideration	Monitoring and/or risk mitigation strategies
Metformin	Metformin-associated lactic acidosis	• Monitor eGFR with increasing frequency as eGFR falls to <60 mL/min/1.73 m^2 • Adjust metformin dose as appropriate per eGFR (see Table 4) • Consider dose reduction in the presence of conditions that predispose patients to hypoperfusion and hypoxemia for eGFR 45–59 mL/min/1.73 m^2 • Discontinue for eGFR <30 mL/min/1.73 m^2 • Institute a sick day protocol
	B_{12} malabsorption	• Monitor patients for vitamin B_{12} deficiency when treated with metformin for >4 years
SGLT2i	Genital mycotic infections	• Counsel on genital hygiene
	Volume depletion	• Monitor for hypovolemia and consider proactive dose reduction of diuretics in patients at high risk • Hold SGLT2i during illness
	Diabetic ketoacidosis	• Educate about signs/symptoms to facilitate early recognition • Monitor blood or urine ketones in the case of very high risk • Institute a sick day protocol • Maintain at least low-dose insulin in insulin-requiring individuals
	Hypoglycemia	• Adjust background glucose-lowering agents (e.g., insulin or sulfonylureas) as appropriate
GLP-1 receptor agonists	Nausea/vomiting/diarrhea	• Educate on tolerability and symptom recognition • Start at lowest recommended dose and titrate slowly
	Hypoglycemia	• Adjust background glucose-lowering agents (e.g., insulin or sulfonylureas) as appropriate

eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide 1; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

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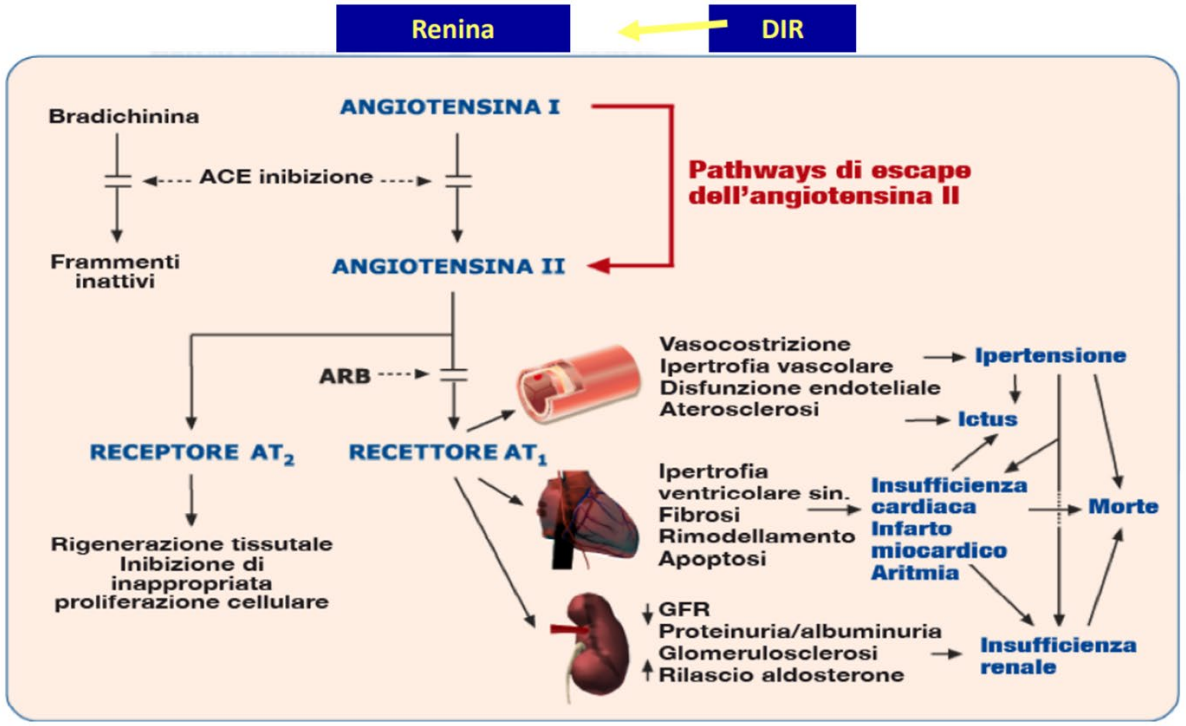
KDIGO Kidney Disease: Improving Global Outcomes

Table 4—Dose adjustments for eGFR <45 mL/min/1.73 m² (information presented reflects the package inserts rather than guidance from this consensus report)

	Stage 3b (eGFR 30–44 mL/min/1.73 m²)	Stage 4 (eGFR 15–29 mL/min/1.73 m²)	Stage 5 (eGFR <15 mL/min/1.73 m²)
Metformin	Reduce dose to 1000 mg/day	Contraindicated	
Insulin	Initiate and titrate conservatively to avoid hypoglycemia		
SGLT2 inhibitors*			
Canagliflozin	Maximum 100 mg daily	Initiation not recommended; may continue 100 mg daily if tolerated for kidney and CV benefit until dialysis	
Dapagliflozin	10 mg daily†	Initiation not recommended with eGFR <25 mL/min/1.73 m²; may continue if tolerated for kidney and CV benefit until dialysis	
Empagliflozin	10 mg daily‡	Initiation not recommended with eGFR <20 mL/min/1.73 m²; may continue if tolerated for kidney and CV benefit until dialysis	
Ertugliflozin	Use not recommended with eGFR <45 mL/min/1.73 m²		
GLP-1 receptor agonists§			
Exenatide	Caution initiating or increasing dose; avoid once-weekly formulation	Use not recommended	
Dulaglutide	No dose adjustment required		
Liraglutide	No dose adjustment required		
Lixisenatide	No dose adjustment required		Use not recommended
Semaglutide	No dose adjustment required		
DPP-4 inhibitors			
Alogliptin	Maximum 12.5 mg daily	Maximum 6.25 mg daily	
Linagliptin	No dose adjustment required		
Saxagliptin	Maximum 2.5 mg daily		
Sitagliptin	Maximum 50 mg daily	Maximum 25 mg once daily	
Sulfonylureas (2nd generation)			
Glimepiride	Initiate conservatively at 1 mg daily and titrate slowly to avoid hypoglycemia		
Glipizide	Initiate conservatively (e.g., 2.5 mg once daily) and titrate slowly to avoid hypoglycemia		
Glyburide	Use not recommended		
Thiazolidinediones			
Pioglitazone	No dose adjustment required		
α-Glucosidase inhibitors			
Acarbose	No dose adjustment required	Use not recommended	
Miglitol	No dose adjustment required	Use not recommended	

TREATMENT TARGETS AND PHARMACOTHERAPY

Blocco farmacologico del sistema RAA con ACE-I e sartani



Consensus Statement

BP Management

- An ACEi or ARB is recommended for patients with T1D or T2D who have hypertension and albuminuria, titrated to the maximum antihypertensive or highest tolerated dose.

1.2. Renin–angiotensin system (RAS) blockade

Recommendation 1.2.1: We recommend that treatment with an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) be initiated in patients with diabetes, hypertension, and albuminuria, and that these medications be titrated to the highest approved dose that is tolerated *(1B)*.

Practice Point 1.2.1: For patients with diabetes, albuminuria, and normal blood pressure, treatment with an ACEi or ARB may be considered.

Practice Point 1.2.2: Monitor for changes in blood pressure, serum creatinine, and serum potassium within 2–4 weeks of initiation or increase in the dose of an ACEi or ARB (Figure 4).

Practice Point 1.2.3: Continue ACEi or ARB therapy unless serum creatinine rises by more than 30% within 4 weeks following initiation of treatment or an increase in dose (Figure 4).

Practice Point 1.2.4: Advise contraception in women who are receiving ACEi or ARB therapy and discontinue these agents in women who are considering pregnancy or who become pregnant.

Practice Point 1.2.5: Hyperkalemia associated with the use of an ACEi or ARB can often be managed by measures to reduce serum potassium levels rather than decreasing the dose or stopping the ACEi or ARB immediately

Practice Point 1.2.6: Reduce the dose or discontinue ACEi or ARB therapy in the setting of either symptomatic hypotension or uncontrolled hyperkalemia despite the medical treatment outlined in Practice Point 1.2.5, or to reduce uremic symptoms while treating kidney failure (estimated glomerular filtration rate [eGFR] <15 ml/min per 1.73 m^2).

Practice Point 1.2.7: Use only one agent at a time to block the RAS. The combination of an ACEi with an ARB, or the combination of an ACEi or ARB with a direct renin inhibitor, is potentially harmful.

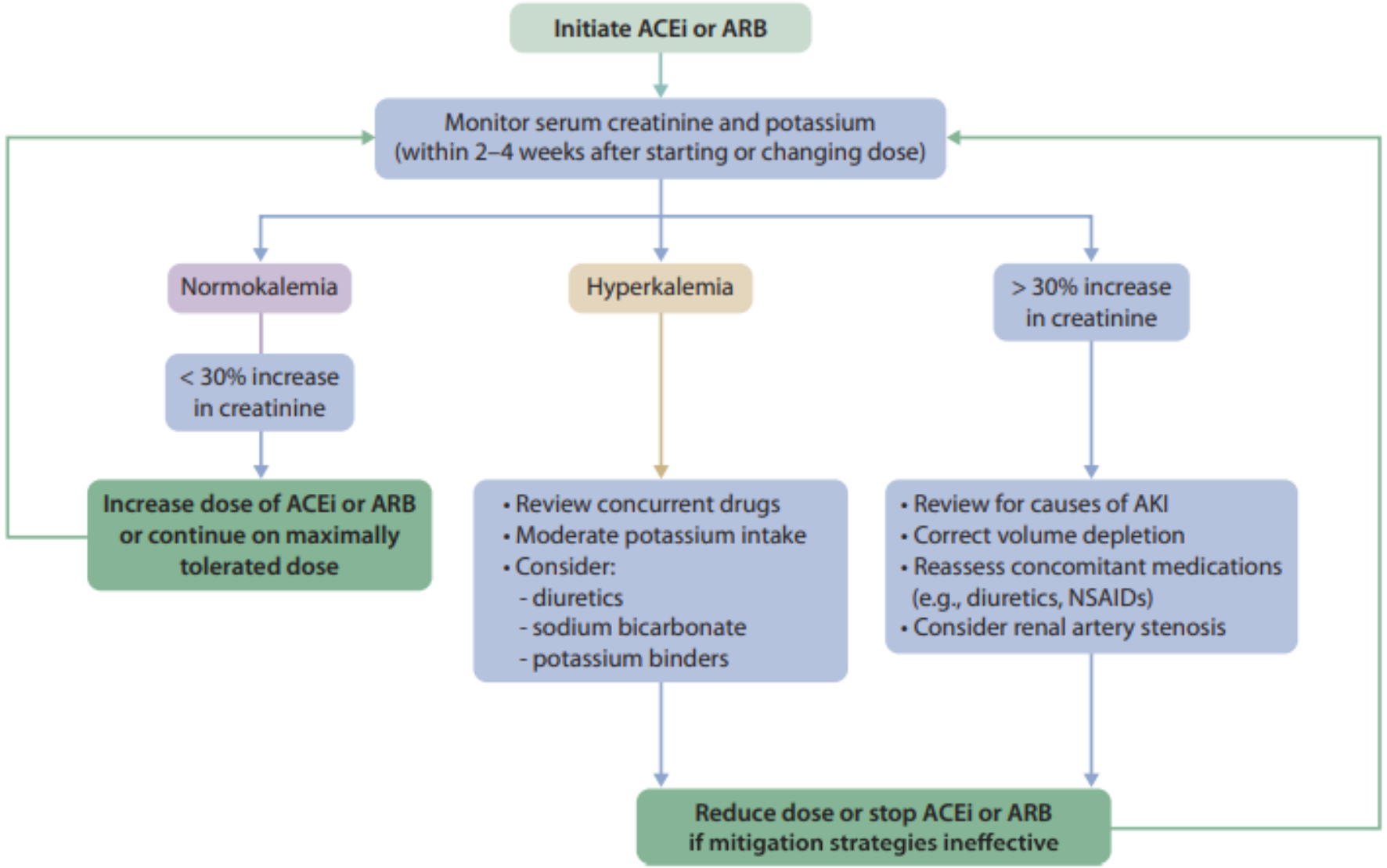
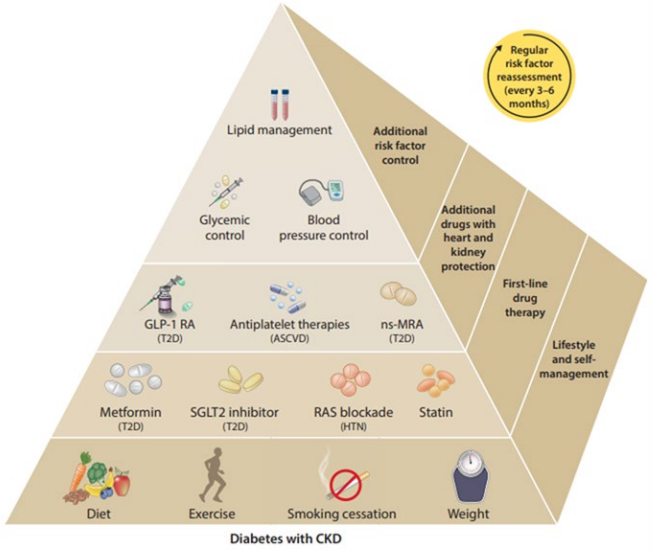


Figure 4 | Monitoring of serum creatinine and potassium during angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) treatment—dose adjustment and monitoring of side effects. AKI, acute kidney injury; NSAID, nonsteroidal anti-inflammatory drug.

TREATMENT TARGETS AND PHARMACOTHERAPY



Consensus Statement

Lipid Management

- A statin is recommended for all patients with T1D or T2D and CKD, moderate intensity for primary prevention of ASCVD or high intensity for patients with known ASCVD and some patients with multiple ASCVD risk factors.

Glucose-Lowering Agents in T2D and CKD

Table 1—Key glucose-lowering agent recommendations for patients with T2D and CKD from ADA and KDIGO (2,17)

Medication class	ADA 2022 Standards of Medical Care in Diabetes	KDIGO 2022 Guideline for Diabetes Management in Chronic Kidney Disease
Metformin	• 9.4a First-line therapy depends on comorbidities, patient-centered treatment factors, and management needs and generally includes metformin and comprehensive lifestyle modification (A).	• Recommendation 4.1.1: We recommend treating patients with T2D, CKD, and an eGFR ≥30 mL/min per 1.73 m^2 with metformin (1B). • Practice Point 4.1.3: Adjust the dose of metformin when the eGFR is <45 mL/min per 1.73 m^2, and for some patients when the eGFR is 45–59 mL/min per 1.73 m^2.

Consensus Statement

Metformin

- Metformin is recommended for patients with T2D, CKD, and eGFR >=30 mL/min/1.73 m2 ; the dose should be reduced to 1,000 mg daily for patients with eGFR 30–44 mL/min/1.73 m2 and for some patients with eGFR 45–59 mL/min/1.73 m2 who are at high risk of lactic acidosis.

4.1. Metformin

Recommendation 4.1.1: We recommend treating patients with T2D, CKD, and an eGFR ≥30 ml/min per 1.73 m^2 with metformin *(1B)*.

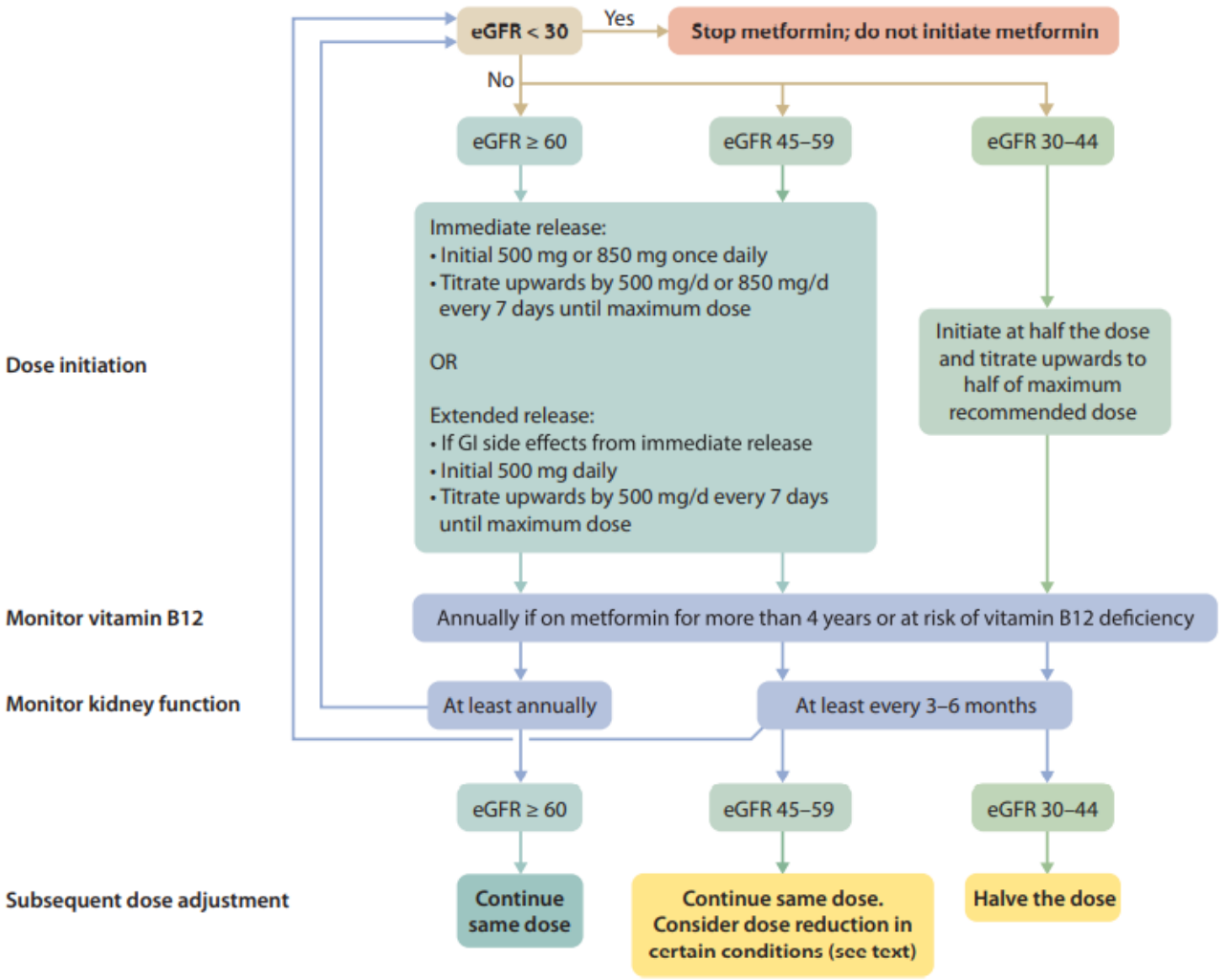
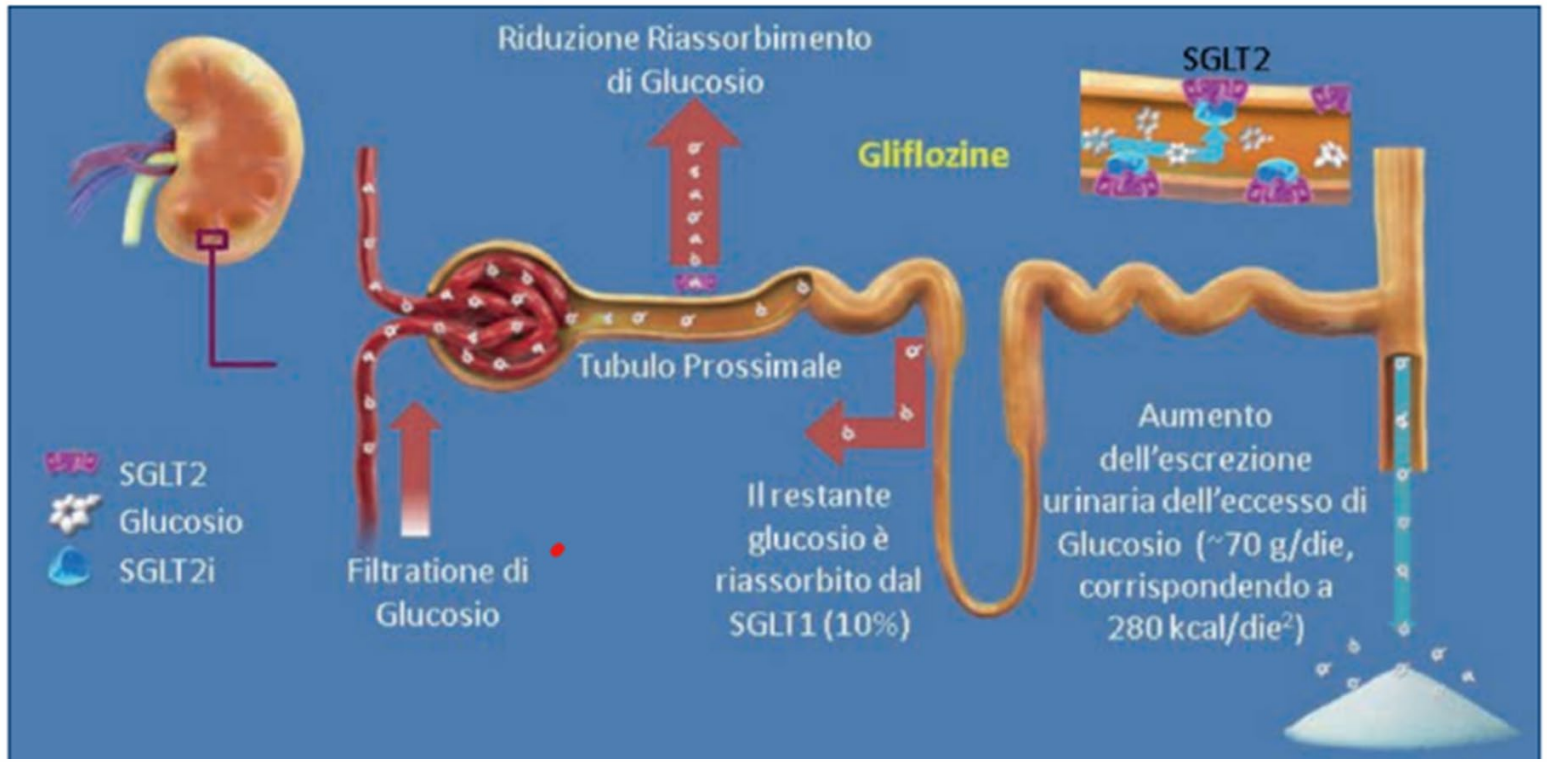


Figure 27 | Suggested approach in dosing metformin based on the level of kidney function. eGFR, estimated glomerular filtration rate (in ml/min per 1.73 m^2); GI, gastrointestinal.

TREATMENT TARGETS AND PHARMACOTHERAPY

Glucose-Lowering Agents in T2D and CKD



Consensus Statement

SGTL2i

- An SGLT2i with proven kidney or cardiovascular benefit is recommended for patients with T2D, CKD, and eGFR >=20 mL/min/1.73 m2 . Once initiated, the SGLT2i can be continued at lower levels of eGFR.

Glucose-Lowering Agents in T2D and CKD

Table 1—Key glucose-lowering agent recommendations for patients with T2D and CKD from ADA and KDIGO (2,17)

Medication class	ADA 2022 Standards of Medical Care in Diabetes	KDIGO 2022 Guideline for Diabetes Management in Chronic Kidney Disease
SGLT2i	• Consider use of SGLT2i for organ protection independent of baseline HbA_{1c}, individualized HbA_{1c} target, or metformin use. • 10.42 Among patients with T2D who have established ASCVD or established kidney disease, an SGLT2i or GLP-1 receptor agonist with demonstrated cardiovascular disease benefit is recommended as part of the comprehensive cardiovascular risk reduction and/or glucose-lowering regimens (A). • 10.42a In patients with T2D and established ASCVD, multiple ASCVD risk factors, or diabetic kidney disease, an SGLT2i with demonstrated cardiovascular benefit is recommended to reduce the risk of MACE and/or HF hospitalization (A). • 11.3a For patients with T2D and diabetic kidney disease, use of an SGLT2i in patients with an eGFR ≥20 mL/min/1.73 m^2 and urinary albumin ≥200 mg/g creatinine is recommended to reduce CKD progression and cardiovascular events (A).* • 11.3b For patients with T2D and diabetic kidney disease, use of an SGLT2i is recommended to reduce CKD progression and cardiovascular events in patients with an eGFR ≥20 mL/min/1.73 m^2 and urine albumin ranging from normal to 200 mg/g creatinine (B).	• Recommendation 1.3.1: We recommend treating patients with T2D, CKD, and an eGFR ≥20 mL/min per 1.73 m^2 with an SGLT2i (1A).

Glucose-Lowering Agents in T2D and CKD

Inizialmente gli SGLT2 inibitori sono stati approvati per il trattamento di soggetti diabetici con HbA1c non a target, nonostante gli interventi sul regime dietetico, le modifiche dello stile di vita e già in terapia con metformina. Erano esclusi i soggetti con GFR < 60 mL/min/1.73m2 , poiché atteso che al ridursi del GFR diminuisce l'effetto glicosurico e così il potere ipoglicemizzante.

Non solo gli SGLT2 si sono confermati sicuri, ma addirittura hanno dimostrato di *ridurre significativamente gli eventi CV maggiori, l'ospedalizzazione per scompenso cardiaco e l'exitus*. Ciò era vero nei soggetti con malattia CV conclamata come anche in coloro che avevano *solo fattori di rischio,* dunque sia in ***prevenzione secondaria che primaria***.

Principio attivo	Associazione	Denominazione	Dose
Empaglifozin	/	Jardiance©	10 mg
			25 mg
	Metformina	Synjardy©	5 mg + 850 mg
			12,5 + 850 mg
			5 + 1000 mg
			12,5 + 850 mg
	Linagliptin	Glyxambi©	10 mg + 5 mg
			25 mg + 5 mg
Canaglifozin	/	Invokana©	100 mg
	Metformina	Vokanamet©	50 + 850 mg
			150 + 1000 mg
			50 + 1000 mg
			150 + 850 mg
Dapaglifozin	/	Forxiga©	10 mg
	Metformina	Xigduo©	5 + 850 mg
			5 + 1000 mg
	Saxagliptin	Qtern©	5 mg + 10 mg
Ertugliflozin	/	Steglatro©	5 mg
			15 mg
	Metformina	Segluromet©	2,5 mg + 850 mg
			2,5 mg + 1000 mg
			7,5 mg + 850 mg
			7,5 mg + 1000 mg
	Sitagliptin	Steglujan©	5 mg + 100 mg
			15 mg + 100 mg

SGLT2 inibitori, non solo ipoglicemizzanti: impatto nella pratica clinica nefrologica

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Glucose-Lowering Agents in T2D and CKD

Toyama et al., hanno condotto una **metanalisi** che ha incluso **27 studi** per un totale di **7363** soggetti diabetici con GFR< 60 mL/min/1.73m2 . Il lavoro concludeva per l'efficacia degli SGLT2 inibitori su più fronti: *miglioramento del controllo della pressione arteriosa sistemica, riduzione del peso corporeo e dell'albuminuria, rallentamento del declino del GFR, riduzione del rischio di scompenso cardiaco, infarto miocardico acuto, ictus cerebri, morte CV, endpoint renale composito (raddoppio creatinina o ESRD o morte renale).*

Lo Studio **CREDENCE** (Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation) è il primo trial randomizzato a doppio cieco realizzato al fine di valutare gli effetti delle glifozine sulla prognosi renale.
Ha reclutato diabetici macroalbuminurici e con GFR 30-90 mL/min/1.73m2 , già in terapia con inibitori dal RAS alla massima dose tollerata. I pazienti sono stati randomizzati a **canaglifozin 100 mg/die** rispetto a placebo ed il tempo di follow-up mediano è stato di 2,62 anni per sospensione anticipata dello studio ad ottobre 2018 per efficacia del trattamento sperimentale.

Canaglifozin ha dimostrato:

- un'azione antiproteinurica (riduzione albuminuria di circa il 31%) protratta anche alla sospensione del farmaco (indotte modificazioni strutturali);
- riduzione del GFR di circa 5 mL/min/1.73m2 nel 1° mese di trattamento; effetto rapido e reversibile alla sospensione del farmaco (modificazioni dell'emodinamica renale dovuta agli SGLT2 inibitori almeno nelle prime fasi.; successivo rallentamento nel declino del GFR con un vantaggio significativo pari a **1,52 mL/min/1.73m2 per anno**, protrattosi per tutto il follow-up;
- ridotto del **34%** il rischio di *endpoint renale composito* (raddoppio della creatinina, eGFR < 15 mL/min/1.73m2 o dialisi per almeno 30 giorni, trapianto o morte renale) nella popolazione in studio e nei soggetti con GFR 30-44 mL/min/1.73m2 , pari al **29%**;
- ridotto il tasso di ospedalizzazione per scompenso cardiaco, gli eventi CV maggiori e la morte CV .

Dekkers et al. hanno analizzato gli ***outcome CV e renali*** nei trial EMPA-REG OUTCOME, CANVAS, DECLARE TIMI-58 e CREDENCE, dividendo i soggetti in quattro sottogruppi per GFR al basale: <45, 45-60, 60-90, > 90 mL/min/1.73m2 .

- *I benefici CV e renali erano mantenuti per tutte le classi di GFR*, pur con delle interessanti differenze.
- I soggetti con funzione renale più compromessa facevano registrare il maggior vantaggio CV.
- Considerando cumulativamente gli outcome CV e renali, ***i sottogruppi con GFR più basso, quelli originariamente esclusi dalla terapia con SGLT2 inibitori, avevano maggior beneficio rispetto ai soggetti con funzione renale normale o lievemente ridotta***.

Sono multipli, diretti e indiretti, locali e sistemici.

- agiscono favorevolmente sul compenso glicemico, *aumentando l'escrezione urinaria di glucosio*, ma anche *migliorando l'utilizzazione epatica del glucosio e riducendo l'insulino-resistenza a livello muscolare*;
- nei diabetici con funzione renale conservata gli SGLT2 inibitori hanno ottenuto una riduzione dell'HbA1c pari a 0,66%. In presenza di MRC, insieme al GFR si riduce l'effetto glicosurico e quindi il potere ipoglicemizzante con diminuzione in HbA1c nello stadio 3A NKF-KDOQI compresa tra 0,33 e 0,37%, mentre nessuna variazione significativa veniva osservata negli stadi 3B e 4 NKF-KDOQI;
- il rallentamento del declino del GFR e la riduzione della proteinuria da SGLT2 inibitori sono *indipendenti* dal controllo glicemico;
- riducono il peso corporeo, il BMI (indice di massa corporea) e la circonferenza vita;
- l'aumento dell'ematocrito, dell'albuminemia e dei livelli ematici e urinari degli ormoni del RAS sono segno della contrazione del volume ematico. L'azione diuretica e natriuretica si attenuano in 3-4 giorni, rendendo conto del 30-40% della riduzione del peso corporeo nel lungo termine;
- l'incrementata eliminazione di acqua e sodio agisce favorevolmente sul controllo della pressione arteriosa sistemica e nel contrastare eventuali condizioni di sovraccarico di volume con aumentato precarico cardiaco.

SGLT2 inibitori – i meccanismi della nefroprotezione

La terapia con SGLT2 inibitori **riduce la pressione arteriosa sistemica**, sia diurna che notturna ed indipendentemente dalla funzione renale.
I meccanismi che sembrano sottendere la riduzione della pressione arteriosa sistemica comprendono ***l'azione diuretica , la diminuzione del peso e del sodio corporeo totale e la riduzione della rigidità della parete dei vasi arteriosi***.

Possibili effetti favorevoli degli SGLT2 inibitori sullo ***stato infiammatorio cronico sia generalizzato che locale***, intraparenchimale renale, propri del soggetto diabetico.
In uno studio in vitro canaglifozin ha ridotto i livelli del recettore 1 del TNF (fattore di necrosi tumorale), interleuchina 6, metalloproteinasi della matrice 7 e fibronectina 1 .
Altri autori hanno riportato che gli SGLT2 inibitori riducono la presenza di radicali liberi dell'ossigeno ed ormoni del RAS nel parenchima renale.

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SGLT2 inibitori – i meccanismi della nefroprotezione

Ulteriore ***azione antinfiammatoria*** è il contrasto alla glucotossicità locale attraverso l'inibizione del riassorbimento massivo di glucosio a livello tubulare. Le glifozine scongiurando l'eccessivo consumo di energia e ossigeno a tal livello, possono combattere l'instaurarsi di una condizione di ipossia, stress ossidativo, flogosi e fibrosi tubulo-interstiziale.
Preservare un'adeguata ossigenazione del parenchima renale garantisce la *differenziazione dei fibroblasti* della corteccia renale nelle cellule produttrici di eritropoietina. In linea, il trattamento con SGLT2 inibitori è risultato associato ad ***aumento della sintesi di eritropoietina***.

La ***podocitopatia*** correla con la comparsa di proteinuria e la progressione del danno renale. Nel modello murino e in vitro, SGLT2 era espresso nei podociti e sovraespresso in presenza di proteinuria. Di grande interesse, dapaglifozin è risultata associata a riduzione del danno e della perdita podocitaria.

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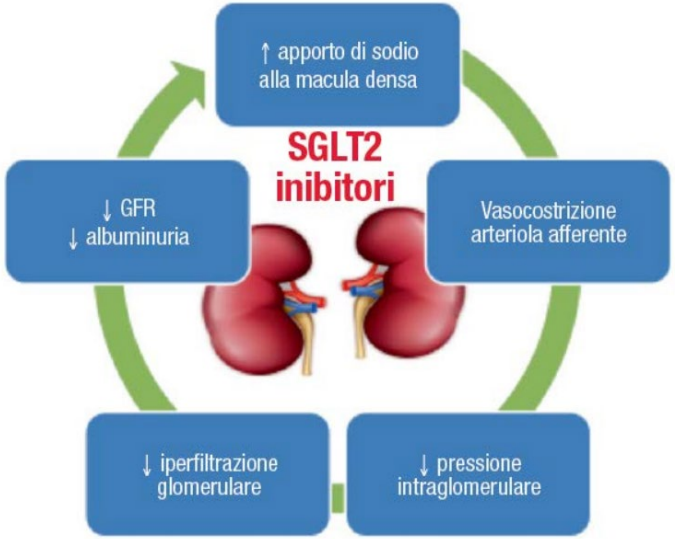
SGLT2 inibitori – i meccanismi della nefroprotezione

De Nicola et al. hanno suggerito che gli SGLT2 inibitori possono contrastare l'iperfiltrazione glomerulare, indipendentemente dall'effetto ipoglicemizzante e addurre benefici relativi ad albuminuria, infiammazione e nefromegalia secondariamente al miglioramento del controllo glicemico.

Una maggiore disponibilità di sodio a livello della macula densa, conseguenza del ridotto riassorbimento nel tubulo prossimale da inibizione SGLT2 inibitori-mediata, conduce a ***ripristino del feedback tubulare-glomerulare:*** *la vasocostrizione dell'arteriola afferente e la vasodilazione dell'arteriola efferente contrastano l'ipertensione e l'iperfiltrazione glomerulare*.

La riduzione della pressione intraglomerulare mediata dal ripristino del feedback tubuloglomerulare, attenuando lo stress di parete, può contribuire agli effetti antinfiammatori degli SGLT2 inibitori .



Azioni degli inibitori di SGLT2 sul sistema vascolare renale.

SGLT2 inibitori, non solo ipoglicemizzanti: impatto nella pratica clinica nefrologica

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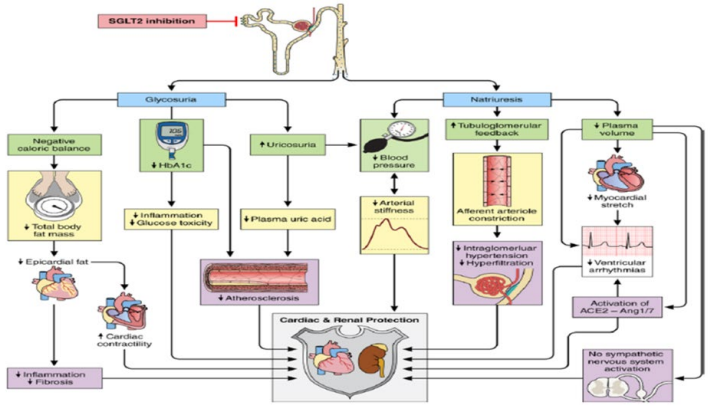
SGLT2 inibitori – i meccanismi della nefroprotezione

Gli SGLT2 inibitori hanno mostrato favorevoli *effetti metabolici non-glicemici* mediati, almeno in parte, dal glucagone. Si è visto che SGLT2 sono presenti nelle alfa cellule del pancreas. L'azione diretta degli SGLT2 inibitori a questo livello determina un ***aumentato rilascio di glucagone***.

A sua volta il glucagone attiva la ***lipolisi*** e la ***mobilizzazione degli acidi grassi dal tessuto adiposo***, come anche la chetogenesi epatica. L'inibizione degli SGLT2 pancreatici mima una condizione di ipoglicemia con attivazione delle vie metaboliche che favoriscono l'utilizzo di nuovi substrati (acidi grassi e chetoni) e il consumo delle riserve adipose (tessuto adiposo e fegato) con effetti positivi in termini di *perdita di peso, sulla steatosi epatica e sull'infiammazione*.

Inoltre, la maggiore disponibilità di substrati energetici potrebbe avere un impatto favorevole sulla salute del miocardio; non da meno la recente evidenza della ***riduzione di tessuto adiposo anche a livello del pericardio***, che correla con il rischio di scompenso cardiaco.

L'inibizione di SGLT2 ha un effetto pleiotropico di protezione cardiorenale



Circulation. 2016;134:752–772. DOI: 10.1161/CIRCULATIONAHA.116.021887

SGLT2 inibitori, non solo ipoglicemizzanti: impatto nella pratica clinica nefrologica

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SGLT2 inibitori – effetti collaterali

- Basso rischio di ipoglicemia
- IVU
- Infezioni genitali e gangrena di Fournier
- Amputazioni piede e gamba; fratture vertebrali
- Chetoacidosi diabetica
- AKI (deplezione di volume, effetto uricosurico, shift ossigenazione midollare ->corticale)

	EMPAREG OUTCOME	CANVAS	DECLARE TIMI-58	CREDENCE
Ipoglicemia	–	–	–	–
Infezioni vie urinarie	–	–	–	–
Infezioni genitali	+	+	+	+
Amputazioni	–	+	–	–
Fratture	–	+	–	–
Chetoacidosi diabetica	–	+	+	+
AKI	–	–	–	–

SGLT2 inibitori, non solo ipoglicemizzanti: impatto nella pratica clinica nefrologica

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Harms

There is an increased risk of ***diabetic ketoacidosis*** conferred by SGLT2i; however, this is generally a rare event in T2D, occurring in < 1 per 1000 patient-years in a prior meta-analysis.

There is an increased risk of ***genital mycotic infections*** with SGLT2i treatment in both men and women that is consistent across all trials. Most of the time, such infections can be managed with topical antifungal medications. Self-care practices, such as daily bathing, may reduce risk of genital mycotic infections.

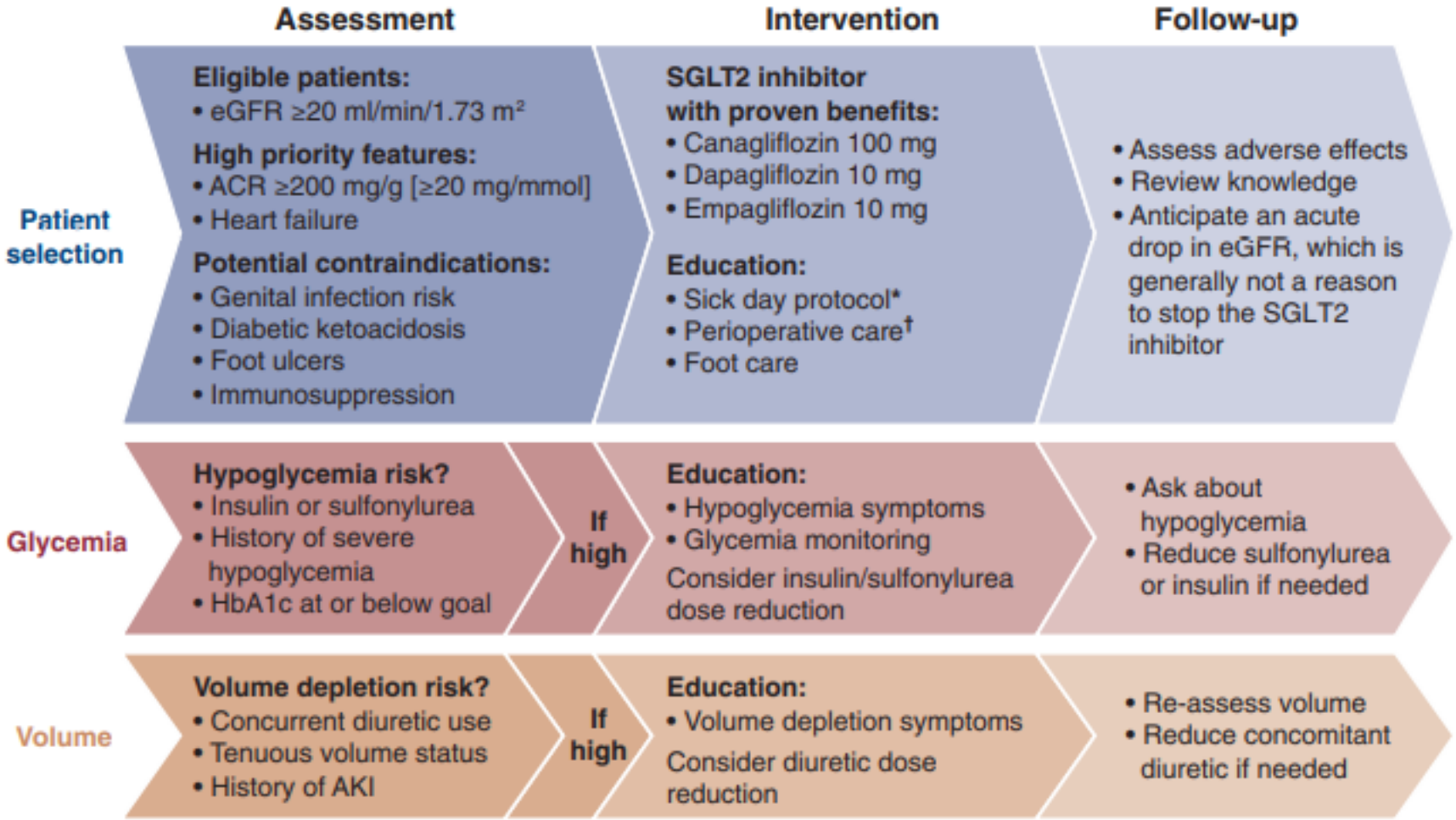
In the CANVAS trial, but not the CANVAS-R trial, there was a higher rate of ***fractures*** attributed to canagliflozin

The increased risk of ***lower-limb amputations*** seen with canagliflozin in the CANVAS trial was not reproduced in the CREDENCE trial,even though this trial did implement special attention to foot care for prevention. This risk of amputations was also not seen with other SGLT2i (empagliflozin and dapagliflozin).

In the DAPA CKD trial, which enrolled exclusively patients with CKD, the incidence of serious adverse events was similar between the dapagliflozin and placebo treated groups. ***No diabetic ketoacidosis or severe hypoglycemia was seen among patients without T2D***

Practice Point 1.3.1: The recommendation for SGLT2i is for kidney and cardiovascular protection and SGLT2i have been shown to have safety and benefit in CKD patients, even for those without T2D. Thus, if patients are already being treated with other glucose-lowering agents, an SGLT2i can be added to the current treatment regimen (Figure 6[148]).

Practical provider guide to initiating SGLT2 inhibitors in patients with type 2 diabetes and CKD



Practice Point 1.3.2: The choice of an SGLT2i should prioritize agents with documented kidney or cardiovascular benefits and take eGFR into account.

SGLT2 inhibitor	Dose	Kidney function eligible for inclusion in pivotal randomized trials	Dosing approved by the US FDA
Dapagliflozin	10 mg daily	eGFR ≥25 ml/min per 1.73 m^2 in DAPA-CKD eGFR ≥30 ml/min per 1.73 m^2 in DAPA-HF and DECLARE	eGFR ≥25 ml/min per 1.73 m^2
Empagliflozin	10 mg daily (Can increase to 25 mg daily if needed for glucose control)	eGFR ≥30 ml/min per 1.73 m^2 in EMPA-REG eGFR ≥20 ml/min per 1.73 m^2 in EMPEROR-Reduced and EMPEROR-Preserved	eGFR ≥30 ml/min per 1.73 m^2 for T2D and ASCVD for glucose control eGFR ≥20 ml/min per 1.73m^2 for HF
Canagliflozin	100 mg daily (The higher dose of 300 mg is not recommended for CKD)	eGFR ≥30 ml/min per 1.73 m^2 in CREDENCE	eGFR ≥30 ml/min per 1.73 m^2

Practice Point 1.3.3: It is reasonable to withhold SGLT2i during times of prolonged fasting, surgery, or critical medical illness (when patients may be at greater risk for ketosis).

For patients with T2D, there is a small but increased risk of euglycemic diabetic ketoacidosis with SGLT2i.

Practice Point 1.3.4: If a patient is at risk for hypovolemia, consider decreasing thiazide or loop diuretic dosages before commencement of SGLT2i treatment, advise patients about symptoms of volume depletion and low blood pressure, and follow up on volume status after drug initiation.

SGLT2i cause an initial natriuresis with accompanying weight reduction. This may contribute to one of the benefits of these drugs, namely, their consistent reduction in risk for heart failure hospitalizations. However, there is theoretical concern for ***volume depletion and AKI***, particularly among patients treated concurrently with diuretics or who have tenuous volume status.

For such patients, *reducing the dose of diuretics* may be reasonable, and follow-up should be arranged to monitor volume status. In older adults, *adequate hydration* should be encouraged.

Practice Point 1.3.5: A reversible decrease in the eGFR with commencement of SGLT2i treatment may occur and is generally not an indication to discontinue therapy.

SGLT2i are associated with overall kidney protection with improved albuminuria, decreased progression to severely increased albuminuria, and reduction of risk from worsening kidney impairment, kidney replacement therapy, or death from kidney causes. Pooled results of the 4 large RCTs that published results on kidney outcomes also demonstrated that risk of AKI is significantly lower with SGLT2i treatment. Therefore, *a modest initial drop in eGFR should not necessitate stopping the SGLT2*

Practice Point 1.3.6: Once an SGLT2i is initiated, it is reasonable to continue an SGLT2i even if the eGFR falls below 20 ml/min per 1.73 m^2, unless it is not tolerated or kidney replacement therapy is initiated.

Protocols of multiple RCTs, including CREDENCE and DAPA-CKD, specified continuation of study drug (active or placebo) even when observed eGFR dropped below the eligibility threshold specified for initiation.
Very few data are available evaluating use of SGLT2i for patients receiving dialysis, and the glucosuric actions of SGLT2i are likely insignificant with this degree of kidney failure. Therefore, it is reasonable to discontinue an SGLT2i prior to initiation of kidney replacement therapy

Practice Point 1.3.7: SGLT2i have not been adequately studied in kidney transplant recipients, who may benefit from SGLT2i treatment, but are immunosuppressed and potentially at increased risk for infections; therefore, the recommendation to use SGLT2i does not apply to kidney transplant recipients (see Recommendation 1.3.1).

Currently, the safety and efficacy of initiating SGLT2i for people with an eGFR < 20 ml/min per 1.73 m2 , in *kidney transplant recipients*, or among individuals with T1D, are not established and are currently being studied; further studies will help clarify the kidney and cardiovascular benefits among these subgroups.

The cardiovascular and kidney benefits appear *independent of glucose-lowering*, suggesting other mechanisms for organ protection, *such as reduction in intraglomerular pressure and single-nephron hyperfiltration leading to preservation of kidney function.*

	KIDNEY TRIALS			CARDIOVASCULAR TRIALS	
	CREDENCE	**DAPA-CKD**	**EMPA-KIDNEY**	**EMPA-REG**	**CANVAS**
Drug	Canagliflozin 100 mg once daily	Dapagliflozin 10 mg once daily	Empagliflozin 10 mg once daily	Empagliflozin 10 mg, 25 mg once daily	Canagliflozin 100 mg, 300 mg once daily
Total of participants	4401	4304	6609	7020	10,142
% with CVD	50	37.4	27	100	66
eGFR criteria for enrollment (ml/min per 1.73 m²)	30–90	25–75	≥20–<45 or ≥45–<90	≥30	≥30
Mean eGFR at enrollment (ml/min per 1.73 m²)	56	43	37.5	74	76
% with eGFR <60	59	88	No information [<45: 5185 (78%); ≥45: 1424 (22%)]	26	20
ACR	Criteria: ACR >300–5000 mg/g [>30–500 mg/mmol] Median ACR 927 mg/g [92.7 mg/mmol]	ACR 200–5000 mg/g [20–500 mg/mmol] ACR Median DAPA: 965 mg/g [96.5 mg/mmol]; Placebo: 934 mg/g [93.4 mg/mmol]	eGFR ≥45–<90: ACR ≥200 mg/g [≥20 mg/mmol] (or PCR ≥300 mg/g [≥30 mg/mmol]) No ACR criteria for eGFR ≥40–<45 Median ACR 412 mg/g [41.2 mg/mmol]	No criteria ACR <30 mg/g [<3 mg/mmol] in 60%; 30–300 mg/g [3–30 mg/mmol] in 30%; >300 mg/g [>30 mg/mmol] in 10%	No criteria Median ACR 12.3 mg/g [1.23 mg/mmol]
Follow-up (yr)	2.6	2.4	Expected ≥3	3.1	2.4
Primary outcome(s)	Composite of kidney failure, doubling of SCr, or death from kidney or CV causes	First occurrence of a ≥50% decline in eGFR, the onset of kidney failure, or death from kidney or CV causes	First occurrence of a composite of kidney disease progression (kidney failure, sustained decline in eGFR to <10 ml/min/1.73 m², sustained decline in eGFR ≥40%, or renal death) or CV death	MACE	MACE
CV outcome results	CV death, MI, stroke: HR: 0.80; 95% CI: 0.67–0.95; hospitalization for HF: HR: 0.61; 95% CI: 0.47–0.80	Secondary composite of CV death or hospitalization for HF: HR: 0.71; 95% CI: 0.55-0.92	Not reported	MACE: HR: 0.86; 95% CI: 0.74–0.99; hospitalization for HF: HR 0.65; 95% CI: 0.50–0.85	MACE: HR: 0.86; 95% CI: 0.75–0.97; hospitalization for HF: HR 0.67; 95% CI: 0.52–0.87
Kidney outcome	Composite of kidney failure, doubling SCr, or death from kidney or CV causes	First occurrence of a ≥50% decline in eGFR, the onset of kidney failure, or death from kidney or CV causes	First occurrence of kidney failure, sustained decline in eGFR to <10 ml/min/1.73 m², sustained decline in eGFR ≥40%, or renal death	Incident or worsening nephropathy (progression to severely increased albuminuria, doubling of SCr, initiation of KRT, or renal death) and incident albuminuria	Composite doubling in SCr, kidney failure, or death from kidney causes
Kidney outcome results	Primary kidney: HR: 0.70; 95% CI: 0.59–0.82	Primary outcome: HR: 0.61; 95% CI: 0.51– 0.72	[Trial stopped early due to positive results]	Incident/worsening nephropathy: 12.7% vs. 18.8% in empagliflozin vs. placebo. [HR: 0.61; 95% CI: 0.53–0.70] Incident albuminuria: NS	Composite kidney: 1.5 vs. 2.8 per 1000 patient-years in the canagliflozin vs. placebo [HR: 0.53; 95% CI: 0.33–0.84]

	CARDIOVASCULAR TRIALS			HEART FAILURE TRIALS				
	DECLARE-TIMI 58	**VERTIS-CV**	**SCORED**	**DAPA-HF**	**EMPEROR-Reduced**	**SOLOIST**	**EMPEROR-Preserved**	**DELIVER**
Drug	Dapagliflozin 10 mg once daily	Ertugliflozin 5mg, 15 mg once daily	Sotagliflozin 200 mg, 400 mg once daily	Dapagliflozin 10 mg once daily	Empagliflozin 10 mg once daily	Sotagliflozin 200 mg, 400 mg once daily	Empagliflozin 10 mg once daily	Dapagliflozin 10 mg once daily
Total of participants	17,160	8246	10,584	4744	3730	1222	5988	6263
% with CVD	41	100	100	100	100	100	100	100
eGFR criteria for enrollment (ml/min per 1.73 m²)	CrCl ≥60, 45% had eGFR 60–90	No criteria	25–60 ml/min per 1.73 m²	≥30	>20	No criteria	No criteria	≥25
Mean eGFR at enrollment (ml/min per 1.73 m²)	85	76	44	66	62	50	61	Not reported
% with eGFR <60	7.4	21.9	100	41	48	69.9	49.9	Not reported
ACR	ACR <30 mg/g [<3 mg/mmol] in 69.1%, ≥30 to ≤300 mg/g [≥3–≤30 mg/mmol] in 23.9%, and >300 mg/g [>30 mg/mmol] in 6.9%	No criteria	No criteria ACR <30 mg/g [3 mg /mmol] in 35%; ACR 30–<300 mg/g [3–<30 mg/mmol] in 34%; ACR ≥300 mg/g [≥30 mg/mmol] in 31%	No criteria	No criteria	No criteria	No criteria	No criteria
Follow-up (yr)	4.2	3.5	1.3	1.5	1.3	0.76	2.2	Expected 2.25
Primary outcome(s)	1) MACE; 2) Composite CV death or hospitalization for HF	MACE	Deaths from CV causes, hospitalizations for HF, and urgent visit for HF	CV death or worsening HF	CV death or hospitalization for HF	Deaths from CV causes and hospitalizations and urgent visits for HF	CV death or hospitalization for HF	Time to first occurrence of: CV death, hospitalization for HF, or urgent HF visit
CV outcome results	MACE: HR: 0.93; 95% CI: 0.84–1.03; CV death or hospitalization for HF: HR: 0.83; 95% CI: 0.73–0.95	MACE: HR: 0.97; 95% CI: 0.85–1.11	Primary outcome: HR: 0.74; 95% CI: 0.63–0.88	Primary outcome: HR: 0.74; 95% CI: 0.65–0.85	Primary outcome: HR: 0.75; 95% CI: 0.65–0.86	Primary outcome: HR: 0.67; 95% CI: 0.52–0.85	Primary outcome: HR: 0.79; 95% CI: 0.69–0.90	[Met primary endpoint]
Kidney outcome	Composite of ≥40% decrease in eGFR to <60 ml/min per 1.73 m², kidney failure, CV or renal death	Composite of kidney death, kidney replacement therapy, or doubling of SCr	First occurrence of a sustained decrease in GFR ≥50% for ≥30 days, long-term dialysis, kidney transplantation, or a sustained eGFR <15 ml/min per 1.73 m² for ≥30 days	Composite of worsening kidney function (sustained decline of eGFR ≥50%, kidney failure, or renal death)	Chronic dialysis or kidney transplant or ≥40% sustained reduction in eGFR or sustained eGFR <15 ml/min per 1.73 m² in patients with a baseline eGFR ≥30 ml/min per 1.73 m² or sustained eGFR of <10 ml/min per 1.73 m² in patients with a baseline GFR of <30 ml/min per 1.73 m²	Not reported	Composite kidney outcome	Not reported
Kidney outcome results	Composite kidney: HR: 0.76; 95% CI: 0.67–0.87	Composite kidney outcome: HR: 0.81; 95% CI: 0.63–1.04	Composite kidney outcome: HR: 0.71; 95% CI: 0.46–1.08	Composite kidney outcome: HR: 0.71; 95% CI: 0.44–1.16	Composite kidney outcome: HR: 0.50; 95% CI: 0.32–0.77	N/A	Composite kidney outcome: HR: 0.95; 95% CI: 0.73–1.24	Not reported

Kidney outcomes

EMPA-REG (empagliflozin vs. placebo) also evaluated a prespecified kidney *outcome of incident or worsening nephropathy*, defined as progression to severely increased albuminuria (ACR >300 mg/g [>30 mg/mmol]), doubling of serum creatinine, accompanied by an eGFR <45 ml/min per 1.73 m2 , initiation of kidney replacement therapy, or death from kidney causes . This incident or worsening nephropathy outcome was lower in the *empagliflozin* group—**12.7%** versus 18.8%.

CANVAS program (overall cohort including those with and without baseline CKD): *canagliflozin* also conferred kidney benefit, with a **27%** lower risk of progression of albuminuria and a **40%** lower risk of a composite kidney outcome (>40% reduction in eGFR, need for kidney replacement therapy, or death from kidney cause).

DECLARE-TIMI 58 trial (*dapagliflozin* vs. placebo): there was a **1.3%** absolute and 24% relative risk reduction in the secondary kidney outcome (a composite of a >40% decrease in eGFR to < 60 ml/min per 1.73 m2 , kidney failure, and cardiovascular death or death from kidney causes).

Kidney outcomes

DAPA-HF trial: the ***secondary outcome of worsening kidney function*** (defined as a sustained >50% reduction in eGFR, kidney failure, or death from kidney causes) occurred in **1.2%** of the dapagliflozin arm and 1.6% of the placebo arm , which was not statistically significant

DAPA-CKD was the second SGLT2i trial with a primary kidney outcome. DAPA-CKD enrolled 4304 participants with or without T2D who had an eGFR 25–75 ml/min per 1.73 m2 and an ACR of 200–5000 mg/g (20–500 mg/mmol) and evaluated a primary outcome of a sustained decline in the estimated GFR of at least 50%, kidney failure, or death from kidney or cardiovascular causes. Over a median of 2.4 years, *dapagliflozin* reduced the primary kidney outcome by **39%** . Findings were similar among patients with and without T2D

Kidney outcomes

2019 meta-analysis pooled data from the EMPA-REG, CANVAS program, and DECLARE-TIMI 58 trials examined kidney outcomes among individuals with and without CKD.92 For those trial participants with an eGFR of 30 to < 60ml7min per 1.73 m2 , SGLT2i reduced the **risk of adverse kidney outcomes** *(composite worsening kidney failure, kidney failure, or death from kidney causes).*

CREDENCE trial, which was the first RCT of an SGLT2i specifically powered for primary kidney outcomes among patients with exclusively albuminuric CKD. The CREDENCE trial enrolled patients with T2D (with an HbA1c level of 6.5%–12.0%) and CKD, defined by an eGFR of 30–90 ml/min per 1.73 m2 with albuminuria (ACR of 300–5000 mg/g [30–500 mg/mmol]), who were receiving standard of care including a maximum tolerated dose of an ACEi or an ARB. In the CREDENCE trial, 50% of patients had established CVD.

Patients were randomized to *canagliflozin 100 mg* daily or placebo and followed for 2.6 years, with the trial stopping early for superiority as recommended by the Data Safety and Monitoring Committee. The primary kidney outcome was defined as a *composite of kidney failure, doubling of serum creatinine, or death from kidney or cardiovascular causes*.

The primary outcome occurred in 43.2 and 61.2 per 1000 patient-years in the canagliflozin and placebo arms respectively, which translated to a ***30% relative reduction in the primary kidney outcome by canagliflozin***.

6,609 PATIENTS

INCLUSION CRITERIA:

- Race-adjusted eGFR of at least 20 but less than 45mL/minute/1.73m²
- Urinary albumin-to-creatinine ratio of at least 200 at screening visit
- Clinically appropriate dose of single agent RAS inhibitor with or without diabetes

EMPAGLIFLOZIN (N=3,304) vs. PLACEBO (N=3,305)

EMPA-KIDNEY

Empagliflozin in Patients With Chronic Kidney Disease

AMERICAN COLLEGE of CARDIOLOGY

International, Randomized, Parallel-Group, Double-Blind, Placebo-Controlled Trial

OBJECTIVE: To evaluate the effect of empagliflozin treatment on the progression of kidney disease and CV disease and to examine the safety profile among participants with chronic kidney disease.

PRIMARY ENDPOINT

The primary outcome, progression of kidney disease or death from CV cause, occurred in 13.1% in the empagliflozin group and 16.9% in the placebo group, p<0.001

SECONDARY ENDPOINT

For Empagliflozin vs. Placebo:

Hospitalization for heart failure or death from CV cause: 4.0% vs. 4.6%, p=0.15

Hospitalization for any cause:
24.8 events/100 patient-years vs. 29.2 events/100 person-years, p=0.003

Death from any cause: 4.5% vs. 5.1%, p=0.21

Progression of kidney disease: 11.6% vs. 15.2%, HR 0.71; 95% CI 0.62–0.81

CONCLUSION

Among patients with chronic kidney disease with or without diabetes, empagliflozin led to a lower risk of progression of kidney disease or death from CV cause than placebo.

The EMPA-KIDNEY Collaborative Group. Empagliflozin in Patients With Chronic Kidney Disease. *N Engl J Med* 2022; Nov 4:[Epub ahead of print].

Developed and reviewed by Neil Keshvani, MD; Dharam J. Kumbhani, MD, SM, FACC; Deepak L. Bhatt, MD, MPH, FACC.

SGTL2i : Kidney and Heart outcomes

Gli effetti degli SGLT2i sugli outcomes cardiovascolari e renali sono ampiamente coerenti fra tutte le molecole e suggeriscono un *effetto di classe*.

E' stato osservato un beneficio maggiore sulla riduzione del rischio di ospedalizzazione per Scompenso (**30%)** e progressione della malattia renale (**40%**). Tali effetti sono indipendenti dalla pregressa ASCVD o malattia renale e coerenti in popolazioni con scompenso o malattia renale a prescindere dal presenza di diabete.

Le stime dell'effetto sul rischio di ospedalizzazione per scompenso erano le più coerenti in tutti gli studi.

Effetti più modesti sulla riduzione dei **MACE** (circa il 10%), con eterogeneità tra gli studi, EMPAREG, CANVAS, CREDENCE, che mostrano effetti benefici e minore efficacia in pazienti con ASCVD.

Riduzione della morte CV solo in EMPAREG e DAPA HF.

Research recommendations

Studies focused on kidney and heart protective benefits of SGLT2i treatment for patients with *T1D*

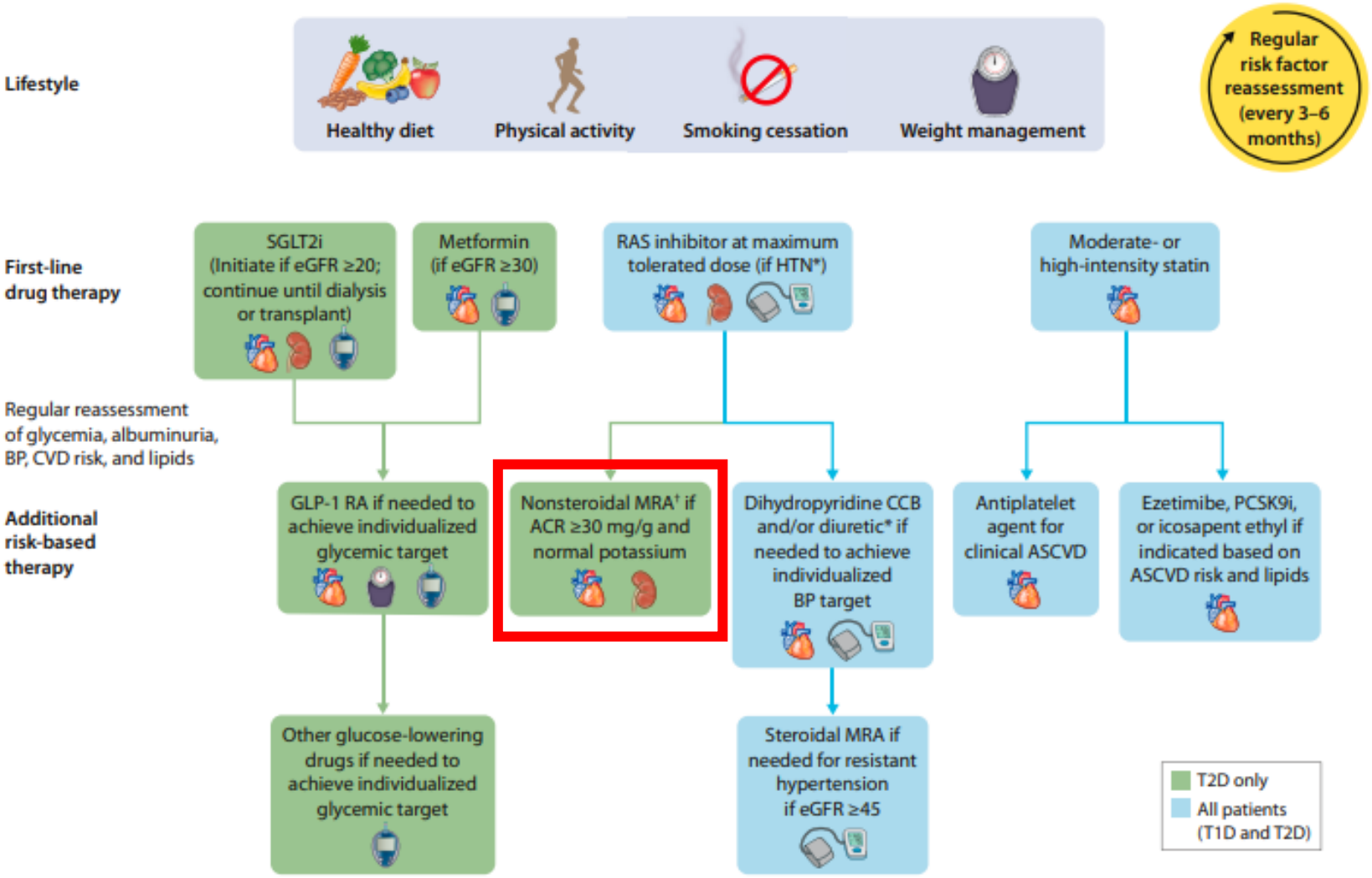
Studies to establish whether there are safety and clinical benefits of SGLT2i for patients with T2D and CKD G5.
Studies examining the safety and benefit of SGLT2i for patients with CKD and eGFR < 20ml/min per 1.73 m2 or *receiving dialysis*.
Studies to establish whether there are safety and clinical benefits of SGLT2i for patients with T2D who are *kidney transplant* recipients at high risk of graft loss, CVD, and infection.

Cost-effectiveness analysis of this strategy prioritizing SGLT2i among patients with T2D and CKD, factoring in cardiovascular and kidney benefits against the cost of medications and potential for adverse effects.

Chapter 1: Comprehensive care in patients with diabetes and CKD

1.1. Comprehensive diabetes and CKD management

Practice Point 1.1.1: Patients with diabetes and chronic kidney disease (CKD) should be treated with a comprehensive strategy to reduce risks of kidney disease progression and cardiovascular disease (Figures 1 and 2).



Recommendation 1.4.1: We suggest a nonsteroidal mineralocorticoid receptor antagonist with proven kidney or cardiovascular benefit for patients with T2D, an eGFR ≥25 ml/min per 1.73 m^2, normal serum potassium concentration, and albuminuria (≥30 mg/g [≥3 mg/mmol]) despite maximum tolerated dose of RAS inhibitor (RASi) *(2A)*.

1.4 Mineralocorticoid receptor antagonists (MRA)

Novel nonsteroidal MRA, such as ***finerenone and esaxerenone***, are more selective for mineralocorticoid receptors and have been noted to offer *similar reductions in albuminuria but with a lower risk of hyperkalemia*. Recently, 2 large clinical trials have examined the cardiovascular and kidney effects of finerenone in those with *T2D and albuminuria, enrolling patients with serum potassium levels less than 4.8 mmol/l at screening*.

The overall quality of the evidence was rated high, as nonsteroidal MRAs exhibited high-quality evidence of benefit for critical composite outcomes of 4-point MACE, the composite kidney outcome, and sustained eGFR >57% or doubling of serum creatinine that are key to clinical decision-making.

ESC European Society of Cardiology European Heart Journal (2022) 43, 474–484 https://doi.org/10.1093/eurheartj/ehab777
FASTTRACK CLINICAL RESEARCH
Diabetes and metabolic disorders

Evidence suggests that overactivation of the mineralocorticoid receptor (MR) leads to inflammation and fibrosis in the heart, kidneys, and vasculature where the MR is extensively expressed that can drive CKD and cardiovascular disease progression. **Finerenone** is a novel, selective, nonsteroidal MR antagonist (MRA) that blocks MRmediated sodium reabsorption and MR overactivation and has demonstrated ***anti-inflammatory and anti-fibrotic effects*** in preclinical kidney and cardiovascular disease models.

FIDELIO-DKD and **FIGARO-DKD,** together, form the largest cardiorenal outcomes programme in CKD in type 2 diabetes to date. They investigated the efficacy and safety of finerenone, on top of maximum tolerated renin–angiotensin system inhibition, on *kidney and cardiovascular outcomes in patients with mild-to-severe CKD in type 2 diabetes.*

In **FIDELIO-DKD**, finerenone significantly reduced the risk of the *primary kidney composite* outcome and the key secondary cardiovascular composite outcome in patients with predominantly stage 3–4 CKD with severely increased albuminuria and type 2 diabetes.

In **FIGARO-DKD**, finerenone significantly reduced the *primary cardiovascular composite outcome* risk in a broader patient population than studied in FIDELIO-DKD (patients with stage 2–4 CKD and moderately increased albuminuria, or stage 1–2 CKD with severely increased albuminuria).

ESC European Society of Cardiology
European Heart Journal (2022) 43, 474–484
https://doi.org/10.1093/eurheartj/ehab777

Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis

Rajiv Agarwal [1*†], Gerasimos Filippatos[2*†], Bertram Pitt [3], Stefan D. Anker[4], Peter Rossing [5,6], Amer Joseph[7], Peter Kolkhof [8], Christina Nowack[9], Martin Gebel [10], Luis M. Ruilope [11,12,13], and George L. Bakris [14]; on behalf of the FIDELIO-DKD and FIGARO-DKD investigators[‡]

Table 1 Pooled analysis study details

Study name	FIDELIO-DKD[7]	FIGARO-DKD[10]
Publication year	2020	2021
Study design	Phase III, randomized, double-blind, placebo-controlled, multicentre clinical trial	Phase III, randomized, double-blind, placebo-controlled, multicentre clinical trial
Sample size[a]	5734	7437
Inclusion criteria	• Age ≥18 years • T2D and CKD defined as UACR 30–<300 mg/g, eGFR 25–<60 mL/min/1.73 m^2, and diabetic retinopathy, *or* UACR 300–5000 mg/g and eGFR 25–<75 mL/min/1.73 m^2 • Maximum tolerated dose of an RAS inhibitor • Serum potassium ≤4.8 mmol/L	• Age ≥18 years • T2D and CKD defined as UACR 30–<300 mg/g and eGFR 25–90 mL/min/1.73 m^2, *or* UACR 300–5000 mg/g and eGFR ≥60 mL/min/1.73 m^2 • Maximum tolerated dose of an RAS inhibitor • Serum potassium ≤4.8 mmol/L
Exclusion criteria	• Non-diabetic kidney disease • Uncontrolled hypertension[b] • HbA1c >12% • SBP <90 mmHg • Chronic symptomatic HFrEF[c] • Recent CV event • Dialysis for acute kidney failure • Kidney transplant	• Non-diabetic kidney disease • Uncontrolled hypertension[b] • HbA1c >12% • SBP <90 mmHg • Chronic symptomatic HFrEF[c] • Recent CV event • Dialysis for acute kidney failure • Kidney transplant
Follow-up period, median	2.6 years	3.4 years
Primary outcome	Time to kidney failure, sustained ≥40% decrease in eGFR from baseline, or renal death	Time to CV death, non-fatal MI , non-fatal stroke, or HHF
Secondary outcome	Time to CV death, non-fatal MI , non-fatal stroke, or HHF	Time to kidney failure, sustained ≥40% decrease in eGFR from baseline, or renal death
Trial registry information	NCT02540993	NCT02545049

1.4 Mineralocorticoid receptor antagonists (MRA)

Practice Point 1.4.1: Nonsteroidal MRA are most appropriate for patients with T2D who are at high risk of CKD progression and cardiovascular events, as demonstrated by persistent albuminuria despite other standard-of-care therapies.

Patients with T2D and albuminuria are known to be at *high risk of CKD progression and cardiovascular events*, and the **FIDELIO-DKD** and **FIGARO-DKD** trials demonstrated that finerenone reduced these events (particularly CKD progression and heart failure) among such patients. Therefore, the most logical application of finerenone is to patients with *high residual risks of CKD progression and cardiovascular events, as evidenced by the presence of albuminuria (ACR >30 mg/g [>3 mg/mmol]) despite lifestyle modifications and first-line drug therapies (RASi, etc).*

Practice Point 1.4.2. A nonsteroidal MRA can be added to a RASi and an SGLT2i for treatment of T2D and CKD.

It is also possible that SGLT2i may reduce the risk of hyperkalemia for patients treated concomitantly with a RASi and nonsteroidal MRA. These data, combined with complementary mechanisms of action, suggest that the *benefits of SGLT2i and finerenone may be additive.*

1.4 Mineralocorticoid receptor antagonists (MRA)

Practice Point 1.4.3: To mitigate risk of hyperkalemia, select patients with consistently normal serum potassium concentration and monitor serum potassium regularly after initiation of a nonsteroidal MRA.

To mitigate this risk, the FIDELIO-DKD and FIGARO-DKD trials restricted eligibility to patients with normal serum potassium concentration (after maximizing RASi) and implemented a standardized potassium-monitoring protocol. These approaches yielded acceptable rates of hyperkalemia with few attributable serious adverse events.

K^+ ≤4.8 mmol/l

- Initiate finerenone
  - 10 mg daily if eGFR 25–59 ml/min per 1.73 m^2
  - 20 mg daily if eGFR ≥60 ml/min per 1.73 m^2
- Monitor K^+ at 1 month after initiation and then every 4 months
- Increase dose to 20 mg daily, if on 10 mg daily
- Restart 10 mg daily if previously held for hyperkalemia and K^+ now ≤5.0 mmol/l

K^+ 4.9–5.5 mmol/l

- Continue finerenone 10 mg or 20 mg
- Monitor K^+ every 4 months

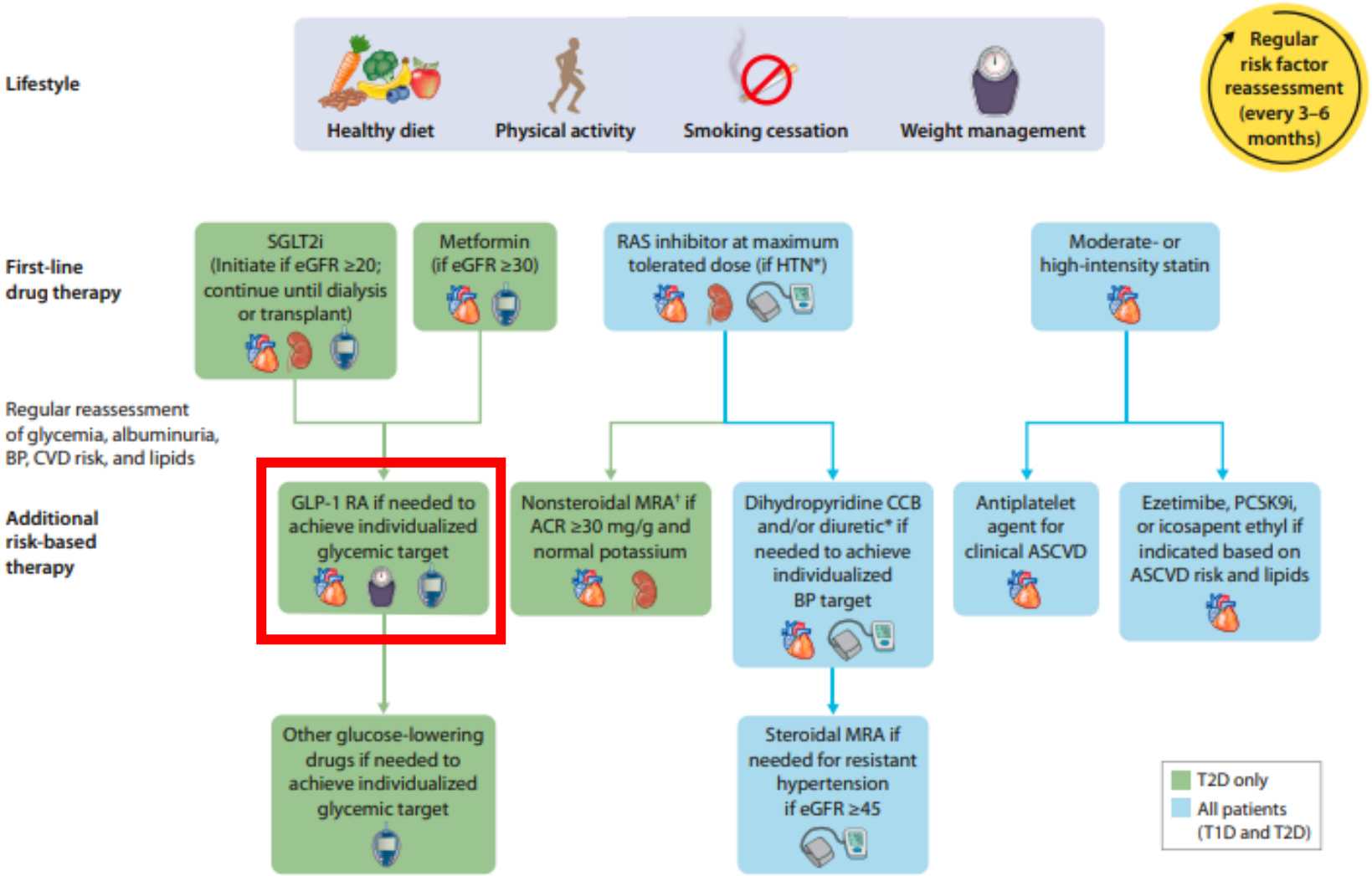
K^+ >5.5 mmol/l

- Hold finerenone
- Consider adjustments to diet or concomitant medications to mitigate hyperkalemia
- Recheck K^+
- Consider reinitiation if/when K^+ ≤5.0 mmol/l

Chapter 1: Comprehensive care in patients with diabetes and CKD

1.1. Comprehensive diabetes and CKD management

Practice Point 1.1.1: Patients with diabetes and chronic kidney disease (CKD) should be treated with a comprehensive strategy to reduce risks of kidney disease progression and cardiovascular disease (Figures 1 and 2).



TREATMENT TARGETS AND PHARMACOTHERAPY

Additional Glucose-Lowering Agents

Table 1—Key glucose-lowering agent recommendations for patients with T2D and CKD from ADA and KDIGO (2,17)

Medication class	ADA 2022 Standards of Medical Care in Diabetes	KDIGO 2022 Guideline for Diabetes Management in Chronic Kidney Disease
GLP-1 receptor agonists	• 10.42 Among patients with T2D who have established ASCVD or established kidney disease, an SGLT2i or GLP-1 receptor agonist with demonstrated cardiovascular disease benefit is recommended as part of the comprehensive cardiovascular risk reduction and/or glucose-lowering regimens (A).	• Recommendation 4.2.1: In patients with T2D and CKD who have not achieved individualized glycemic targets despite use of metformin and SGLT2i treatment, or who are unable to use those medications, we recommend a long-acting GLP-1 receptor agonist (1B).

Practice Point 4.2.1: The choice of GLP-1 RA should prioritize agents with documented cardiovascular benefits.

Practice Point 4.2.2: To minimize gastrointestinal side effects, start with a low dose of GLP-1 RA, and titrate up slowly

Practice Point 4.2.3: GLP-1 RA should not be used in combination with dipeptidyl peptidase-4 (DPP-4) inhibitors.

Practice Point 4.2.4: The risk of hypoglycemia is generally low with GLP-1 RA when used alone, but risk is increased when GLP-1 RA is used concomitantly with other medications such as sulfonylureas or insulin. The doses of sulfonylurea and/or insulin may need to be reduced.

Practice Point 4.2.5: GLP-1 RA may be preferentially used in patients with obesity, T2D, and CKD to promote intentional weight loss.

Dulaglutide	0.75 mg and 1.5 mg once weekly	No dosage adjustment Use with eGFR >15 ml/min per 1.73 m^2
Exenatide	10 µg twice daily	Use with CrCl >30 ml/min
Exenatide extended-release	2 mg once weekly	Use with eGFR >45 ml/min per 1.73 m^2
Liraglutide	1.2 mg and 1.8 mg once daily	No dosage adjustment Limited data for severe CKD
Lixisenatide	10 µg and 20 µg once daily	No dosage adjustment Limited data for severe CKD Not recommended with eGFR <15 ml/min per 1.73 m^2
Semaglutide (injection)	0.5 mg and 1 mg once weekly	No dosage adjustment Limited data for severe CKD
Semaglutide (oral)	3 mg, 7 mg, or 14 mg daily	No dosage adjustment Limited data for severe CKD

Ruolo fisiologico delle INCRETINE

Dopo l'ingestione di un pasto, il glucosio presente all'interno del lume intestinale incrementa la sintesi e il rilascio in circolo di GLP-1 (Glucagon-Like Peptide 1) stimolando l'attività del sodium-glucose co-transporter 1 (SGLT-1) espresso sulla membrana delle cellule L del sistema entero-endocrino. Il GLP-1 interagisce con il suo recettore (GLP-1R) espresso sulle cellule β e δ pancreatiche, dove promuove la ***biosintesi e il rilascio di insulina e di somatostatina***, rispettivamente. La somatostatina, a sua volta, è in grado di inibire la secrezione di glucagone da parte delle cellule α pancreatiche per mezzo del recettore della somatostatina 2 (SSTR2).
In modelli sperimentali di diabete, GLP-1 si è dimostrato capace di ***inibire l'apoptosi delle cellule β e promuoverne la proliferazione*** attraverso il reclutamento di precursori cellulari, contribuendo così ad implementare la disponibilità di cellule β attive dal punto di vista funzionale.

L'attivazione del GLP-1R nei centri regolatori della fame a livello ipotalamico ***favorisce la perdita di peso e riduce l'intake di cibo***. L'attività coordinata di encefalo, sistema nervoso autonomo e sistema nervoso enterico è riconosciuta come "asse intestino-cervello" (gut-brain axis). Durante il pasto, il GLP-1 stimola le fibre sensitive del nervo vago mediante l'interazione con GLP-1R a livello del tratto intraepatico della vena porta. Il segnale giunge al nucleo del tratto solitario (NTS), situato nel rombencefalo, da cui partono fibre efferenti che agiscono a livello epatico ***inibendo la gluconeogenesi e riducendo la steatosi e la fibrosi,*** e a livello del tubo digerente ***rallentando la velocità di svuotamento gastrico e la peristalsi del piccolo intestino***. Il risultato finale sarà un aumentato senso di sazietà e la riduzione dell'appetito.

GIN 2021, A. Granata et al.

Ruolo fisiologico delle INCRETINE

Il legame tra GLP-1 e GLP-1R *incrementa il metabolismo e il consumo energetico a livello delle cellule del tessuto adiposo bruno* indipendentemente dall'attività motoria e, contestualmente, *riduce i depositi lipidici nel tessuto adiposo bianco* mediante pathways di trasduzione del segnale che coinvolgono fibre del sistema nervoso simpatico.

Dopo circa 1-2 minuti dalla sua immissione in circolo, il GLP-1 viene rapidamente degradato a peptide inattivo dall'enzima dipeptidil-peptidasi 4 (DPP-4). Grazie alla sua breve emivita, l'azione modulatrice del GLP-1 sul controllo glicemico è calibrata e proporzionale al carico di glucosio introdotto con la dieta, pertanto previene situazioni di ipersecrezione di insulina e conseguenti pericolose ipoglicemie.

GIN 2021, A. Granata et al.

I GLP-1RA inducono la stimolazione sovra-fisiologica del GLP-1R, mimando il meccanismo d'azione del GLP-1 endogeno e amplificandone gli effetti sia locali che sistemici senza interferire in alcun modo con il GIP.
Una caratteristica peculiare riguarda la capacità di aumentare la secrezione insulinica in modalità proporzionale ai valori glicemici: man mano che la glicemia diminuisce, infatti, la secrezione di insulina si riduce. Questo ***meccanismo insulinotropico glucosio-dipendente*** spiega la bassa incidenza di eventi ipoglicemici associati alla terapia con GLP-1RA, sia quando sono utilizzati da soli che in duplice o triplice terapia con metformina, sulfoniluree, pioglitazone o insulina.

Incretino-mimetici: Exenatide, Exenatide LAR, Lixisenatide: mostrano un effetto più marcato sul rallentamento dello svuotamento gastrico, che si traduce in una maggiore riduzione dell'incremento glicemico post-prandiale, mentre sono meno efficaci sul controllo della glicemia a digiuno, della secrezione basale di insulina e sul mantenimento di valori stabili di emoglobina glicata (HbA1c). L'eliminazione di questi farmaci avviene principalmente mediante filtrazione glomerulare, riassorbimento tubulare e conseguente degradazione proteolitica, pertanto il loro utilizzo è ***controindicato in presenza di eGFR <30 ml/min/1,73m2.***

Analoghi del GLP-1 umano: Liraglutide, Dulaglutide, Semaglutide iniettabile, Semaglutide orale, Albiglutide (non più in commercio): presentano un *basso potere immunogeno* in virtù di un'elevata analogia strutturale con il GLP-1 endogeno. La loro *lunga emivita* è indotta da specifiche caratteristiche molecolari, quali il legame covalente con l'albumina (albiglutide), con la porzione Fc dell'immunoglobulina (Ig) umana G4 (dulaglutide) o con specifici acidi grassi (liraglutide), che ne impediscono l'eliminazione per via renale. A seguito di ciò, gli analoghi del GLP-1 umano possono essere utilizzati con sicurezza anche a fronte di valori di *eGFR fino a 15 ml/min/1,73m2 .*

Essi inducono una riduzione più marcata della HbA1c e della glicemia a digiuno e diminuiscono l'incidenza di effetti collaterali quali nausea e vomito; inoltre, hanno dimostrato una ***maggiore efficacia sulla mortalità e la morbidità cardiovascolare .***

I GLP-1RA richiedono generalmente la *somministrazione sottocutanea*.

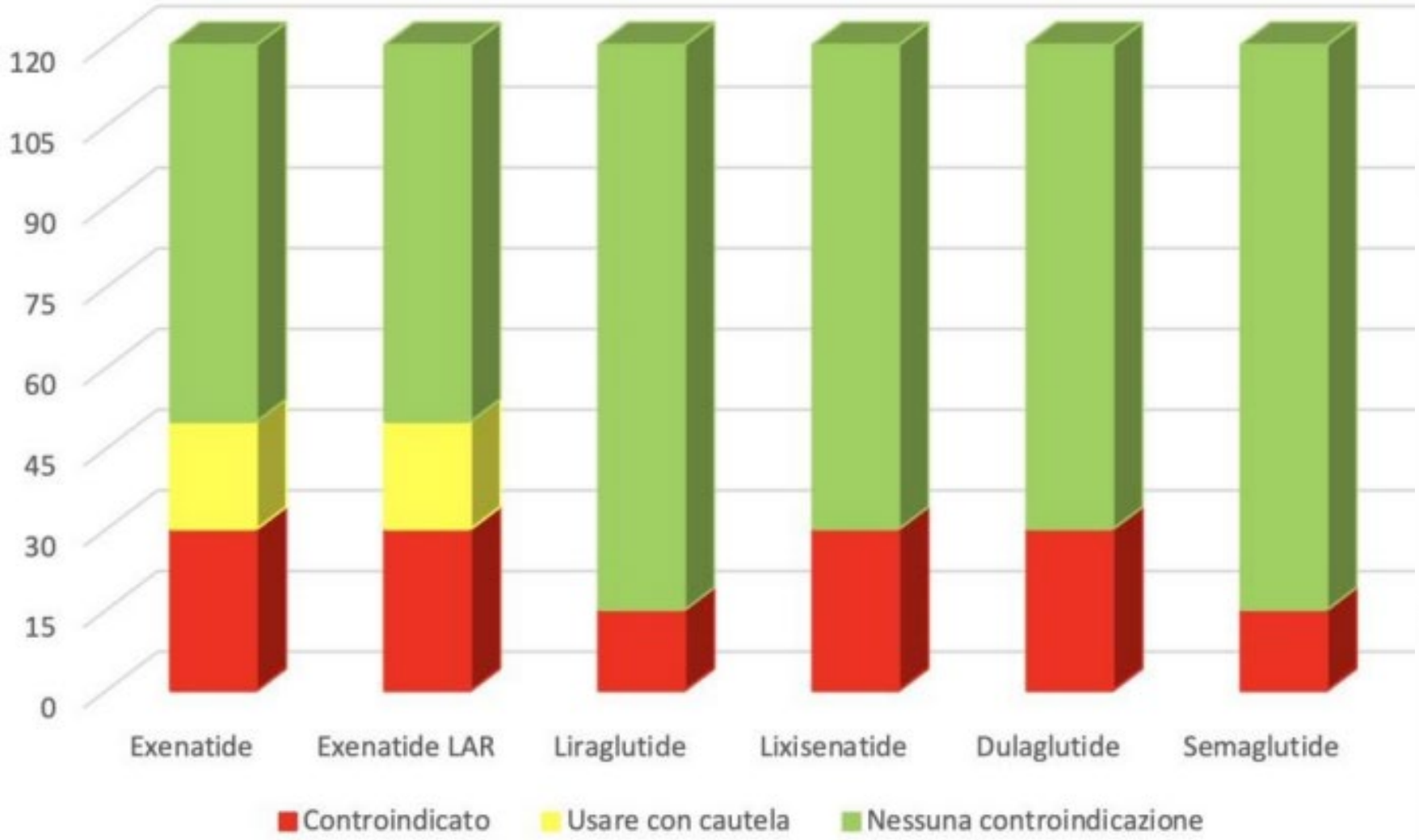


Figura 2: Adeguamento posologico dei GLP-1RA in base al eGFR (espresso in ml/min/1,73 m2)

GIN 2021, A. Granata et al.

EFFETTI DIRETTI	EFFETTI INDIRETTI
▪ Aumentano la diuresi e la natriuresi	▪ Migliorano il controllo glicemico
▪ Ripristinano il normale funzionamento del feedback tubulo-glomerulare	▪ Migliorano il controllo pressorio
▪ Sopprimono l'iperattivazione del sistema renina-angiotensina-aldosterone	▪ Favoriscono la perdita di peso
▪ Abbassano la concentrazione sierica di angiotensina II	▪ Aumentano la sensibilità tissutale all'insulina
▪ Inibiscono l'espansione mesangiale e la fibrosi renale	▪ Riducono la produzione post-prandiale di glucagone
▪ Minimizzano il danno ipossico-ischemico renale	▪ Riducono l'uptake intestinale dei lipidi
▪ Prevengono il danno ossidativo e la formazione di radicali liberi dell'ossigeno	▪ Modificano il microbiota intestinale (?)

Tabella II: Azione nefroprotettiva dei GLP-1RA

GIN 2021, A. Granata et al.

Dal 2020 è disponibile il primo GLP-1RA (semaglutide) in formulazione ***orale***, per la quale è prevista la mono somministrazione giornaliera.

La serie di trials **PIONEER** ha dimostrato che semaglutide orale, messa a confronto con diverse altre classi di farmaci (SGLT-2 inibitore, inibitore di DPP-4, un altro GLP-1RA, insulina, placebo), ha un ***impatto positivo sui livelli medi di HbA1c, sulla riduzione ponderale e sul profilo di rischio cardiovascolare sia quando usata in mono terapia che in combinazione con metformina ± sulfonilurea***. Sulla base dei dati finora raccolti, la compromissione della funzionalità renale, anche di grado severo, non influisce in modo significativo sulla farmacocinetica di semaglutide; il farmaco non è tuttavia raccomandato nei pazienti con nefropatia terminale.

Dimostrato la presenza di GLP-1R sia nel *glomerulo che nel tubulo renale*.
Contrastano l'iperfiltrazione glomerulare in quanto inducono un ***aumento della diuresi e della natriuresi*** mediante fosforilazione e conseguente inibizione diretta dello scambiatore sodio-idrogeno 3 (NHE3), localizzato sull'orletto a spazzola delle cellule tubulari prossimali.
Liraglutide promuove la natriuresi anche attraverso ***un'aumentata secrezione di atrial natriuretic peptide (ANP***) da parte dei cardiomiociti.
Tali meccanismi spiegano almeno in parte la *correlazione tra assunzione cronica dei GLP-1RA e abbassamento dei valori di pressione arteriosa.*
L'aumentato carico filtrato di sodio che giunge alla macula densa ripristina il ***normale funzionamento del feedback tubulo-glomerulare***, sopprime l'iperattivazione del sistema renina-angiotensina-aldosterone e abbassa la concentrazione sierica di angiotensina II.
Inibiscono l'espansione mesangiale, riducono l'espressione a livello endoteliale di molecole pro-fibrotiche e aumentano la disponibilità di ossido nitrico intraglomerulare, rallentando quindi la progressione della DKD.
Il declino del filtrato glomerulare e la microalbuminuria nei pazienti diabetici fanno parte di un corollario di segni e sintomi sistemici accomunati dalla dislipidemia e dall'aterosclerosi.

GLP-1RA conferiscono nefroprotezione attraverso varie ***proprietà anti-aterogeniche***:

• Riducono la produzione e la secrezione dei *chilomicroni intestinali* con effetti benefici sui livelli plasmatici di colesterolo totale, LDL e trigliceridi;

• Minimizzano il danno ipossico-ischemico renale in quanto regolarizzano l'attività mitocondriale delle cellule renali ;

• Prevengono il danno ossidativo e la formazione di radicali liberi dell'ossigeno (ROS) in quanto aumentano i livelli di cAMP e l'attività della protein-chinasi A, mentre riducono l'attività della NAD(P)H ossidasi, interferiscono con l'espressione dei recettori per i prodotti di glicazione avanzata (AGEs) e sopprimono la via di trasduzione del segnale mediata da F-Kb.

GIN 2021, A. Granata et al.

Uno studio condotto su modello animale ha comparato gli e*ffetti di liraglutide e di saxagliptin sulla composizione del microbiota intestinale*.
Gli autori hanno osservato che liraglutide (ma non saxagliptin) determina una minore espressione dei filotipi correlati all'obesità (tra cui roseburia, erysipelotrichaceae incertae sedis, marvinbryantia, and parabacteroides), mentre al contrario *promuove la crescita dei filotipi blautia e coprococcus* che sono correlati a un BMI più basso. Una possibile spiegazione deriva dal fatto che liraglutide induce un aumento dei livelli di GLP-1 da 4 a 6 volte superiore rispetto all'inibitore di DPP-4, con significative ripercussioni sul rallentamento dello svuotamento gastrico e del transito intestinale. *Tutto ciò contribuisce a modificare il pH e la concentrazione dei diversi nutrienti all'interno del lume intestinale, entrambi fattori determinanti la composizione finale del microbiota.*
In atto, il meccanismo attraverso cui l'influenza dei GLP-1RA sul microbiota intestinale possa migliorare gli outcomes clinici dei pazienti diabetici è ancora tutto da dimostrare.

Nome dello studio	Farmaco	Endpoint renale	Risultati
LEADER	Liraglutide vs placebo	– Macroalbuminuria – Raddoppio della sCreat – eGFR <45 ml/min/1,73 m^2 – Necessità di dialisi – Morte per cause renali	– Minore incidenza di nefropatia – Impatto favorevole sulla macroalbuminuria – Declino del eGFR più lento nei pazienti con IRC moderata/severa
SCALE	Liraglutide vs placebo	– Variazioni di UACR	– Maggiore effetto sulla riduzione della UACR
LIRA-RENAL	Liraglutide vs placebo	– Variazioni di eGFR – Variazioni di UACR	– Nessuna differenza su eGFR e UACR
SUSTAIN – 6	Semaglutide vs placebo	– Macroalbuminuria persistente – Raddoppio della sCreat – eGFR <45 ml/min/1,73 m^2 – Necessità di dialisi	– Minor incidenza di macroalbuminuria *de novo* – Nessuna differenza su incidenza di ESRD e morte per cause renali
ELIXA	Lixisenatide vs placebo	– Variazioni di UACR	– Rallentata progressione della UACR indipendentemente dall'albuminuria basale – Nessuna differenza sul declino del eGFR
EXCEL	Exenatide LAR vs placebo	– Declino del eGFR del 40% – Necessità di dialisi – Morte per causa renale – Macroalbuminuria *de novo*	– Miglioramento dell'*outcome* composito renale – Minor incidenza di macroalbuminuria
AWARD-7	Dulaglutide vs glargine	– Variazioni di eGFR e UACR rispetto al baseline	– Rallentamento del declino del eGFR – Nessuna differenza sulle variazioni di UACR
REWIND	Dulaglutide Vs Placebo	– Macroalbuminuria de novo – Declino del ≥30% rispetto al basale – Necessità di dialisi	– Minore incidenza di macroalbuminuria – Nessuna differenza su declino del eGFR e sulla necessità di dialisi

sCreat: creatinina sierica
eGFR: velocità di filtrazione glomerulare
UACR: rapporto albumina/creatinina urinarie

Tabella III: Rassegna dei principali trials clinici che hanno analizzato l'impatto dei GLP-1RA sugli outcomes renali

I GLP-1RA possiedono un ottimo profilo di sicurezza e hanno dimostrato un ***impatto positivo sulla riduzione del rischio cardiovascolare***. I risultati dei trials clinici finora pubblicati confermano:

- I GLP-1RA presentano un'azione ***nefroprotettiva***, che si estrinseca attraverso effetti sia indiretti (*miglioramento del controllo pressorio e glicemico, perdita di peso*) che diretti (*ripristino di una normale emodinamica intrarenale, prevenzione del danno ischemico e ossidativo*);
- la *riduzione dell'incidenza di albuminuria* e nel *rallentamento del declino della funzionalità renale*:
- Il vantaggio rispetto al trattamento insulinico grazie a un *minor tasso di effetti collaterali avversi*, una migliore *aderenza terapeutica* da parte dei pazienti e agli effetti benefici sul *peso corporeo*.

- Ulteriori studi sono necessari al fine di ampliare le conoscenze sugli effetti nefroprotettivi dei GLP-1RA e sulla loro capacità di implementare a lungo termine gli outcomes cardiovascolari e renali dei pazienti diabetici e, più in generale, dei pazienti con CKD.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

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CONCLUSIONS

In patients with type 2 diabetes who were at high cardiovascular risk, the rate of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke was significantly lower among patients receiving semaglutide than among those receiving placebo, an outcome that confirmed the noninferiority of semaglutide. (Funded by Novo Nordisk; SUSTAIN-6 ClinicalTrials.gov number, NCT01720446.)

Use of Glucagon-Like Peptide 1 Receptor Agonists and Risk of Serious Renal Events: Scandinavian Cohort Study

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OBJECTIVE

To assess the association between use of glucagon-like peptide 1 (GLP-1) receptor agonists and risk of serious renal events in routine clinical practice.

RESEARCH DESIGN AND METHODS

This was a cohort study using an active-comparator, new-user design and nationwide register data from Sweden, Denmark, and Norway during 2010–2016. The cohort included 38,731 new users of GLP-1 receptor agonists (liraglutide 92.5%, exenatide 6.2%, lixisenatide 0.7%, and dulaglutide 0.6%), matched 1:1 on age, sex, and propensity score to a new user of the active comparator, dipeptidyl peptidase 4 (DPP-4) inhibitors. The main outcome was serious renal events, a composite including renal replacement therapy, death from renal causes, and hospitalization for renal events. Secondary outcomes were the individual components of the main outcome. Hazard ratios (HRs) were estimated using Cox models and an intention-to-treat exposure definition. Mean (SD) follow-up time was 3.0 (1.7) years.

RESULTS

Mean (SD) age of the study population was 59 (10) years, and 18% had cardiovascular disease. A serious renal event occurred in 570 users of GLP-1 receptor agonists (incidence rate 4.8 events per 1,000 person-years) and in 722 users of DPP-4 inhibitors (6.3 events per 1,000 person-years, HR 0.76 [95% CI 0.68–0.85], absolute difference −1.5 events per 1,000 person-years [−2.1 to −0.9]). Use of GLP-1 receptor agonists was associated with a significantly lower risk of renal replacement therapy (HR 0.73 [0.62–0.87]) and hospitalization for renal events (HR 0.73 [0.65–0.83]) but not death from renal causes (HR 0.72 [0.48–1.10]). When we used an as treated exposure definition in which patients were censored at treatment cessation or switch to the other study drug, the HR for the primary outcome was 0.60 (0.49–0.74).

CONCLUSIONS

In this large cohort of patients seen in routine clinical practice in three countries, use of GLP-1 receptor agonists, as compared with DPP-4 inhibitors, was associated with a reduced risk of serious renal events.

1.5 Smoking cessation

Recommendation 1.5.1: We recommend advising patients with diabetes and CKD who use tobacco to quit using tobacco products *(1D)*.

The cardiovascular benefits of smoking cessation and the feasibility of making attempts to stop smoking were judged to be the most important aspects to patients. The Work Group also considers it important for patients to address smoking cessation during routine clinical visits despite competing issues that have to be addressed during office visits.

In the judgment of the Work Group, the well-documented clinical benefits of tobacco abstinence, and the availability of various interventions in nearly all settings, justify a *strong recommendation.*

3.2. Physical activity

Recommendation 3.2.1: We recommend that patients with diabetes and CKD be advised to undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance *(1D)*.

Practice Point 3.2.1: Recommendations for physical activity should consider age, ethnic background, presence of other comorbidities, and access to resources.

Practice Point 3.2.2: Patients should be advised to avoid sedentary behavior.

Practice Point 3.2.3: For patients at higher risk of falls, healthcare providers should provide advice on the intensity of physical activity (low, moderate, or vigorous) and the type of exercises (aerobic vs. resistance, or both).

Practice Point 3.2.4: Physicians should consider advising/encouraging patients with obesity, diabetes, and CKD to lose weight, particularly patients with eGFR ≥30 ml/min per 1.73 m^2.

3.1. Nutrition intake

Patients with advanced CKD may naturally decrease their oral intake, leading to ***malnutrition.*** It may be desirable to increase protein intake recommendations in certain individuals. Additionally, protein intake on a diabetic diet is especially crucial to avoid episodes of hypoglycemia; limiting it in the diet may make such potentially dangerous episodes more common.

Weight (kg)	35	40	50	55	60	65	70	75	80	85	90	95	100
Grams of protein per day (wt × 0.8 g/kg)	28	32	40	44	48	52	56	60	64	68	72	76	80

Figure 16| Protein guideline for adults with diabetes and chronic kidney disease (CKD) not treated with dialysis. wt, weight.

Animal proteins

Meat, poultry, fish, seafood, eggs:
28 g (1 oz) = 6–8 g protein
1 egg = 6–8 g protein

Dairy, milk, yogurt, cheese:
250 ml (8 oz) = 8–10 g protein
28 g (1 oz) cheese = 6–8 g protein

Plant proteins

Legumes, dried beans, nuts, seeds:
100 g (0.5 cup) cooked = 7–10 g protein

Whole grains, cereals:
100 g (0.5 cup) cooked = 3–6 g protein

Starchy vegetables, breads:
2–4 g protein

Some diets advocate protein intake greater than 0.8 g/kg/d, especially to reduce carbohydrate intake or promote weight loss. However, long-term effects of ***high-protein diets*** (especially >1.0 g/kg/d) on kidney function are not known and could potentially cause harm by requiring increased kidney excretion of amino acids. A high protein intake could also increase acid load and precipitate or *worsen metabolic acidosis*, particularly in those with lower levels of kidney function.

Dietary recommendations should take into account individual nutrition needs such as age, weight, physical activity, and comorbidities, including for those patients who may need a higher protein diet at early stages to allow for a reduction of carbohydrates to better manage their diabetes.

Chapter 4: Glucose-lowering therapies in patients with T2D and CKD

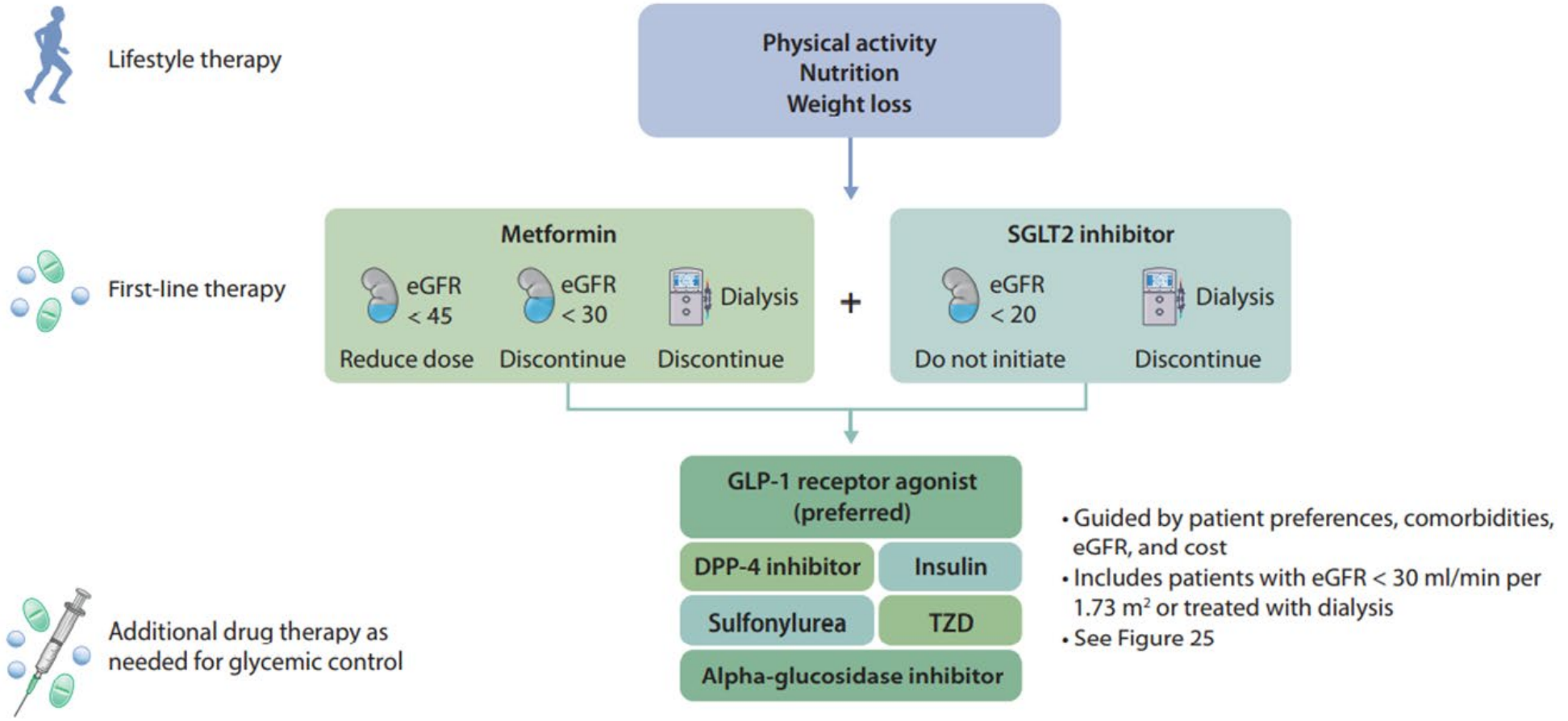
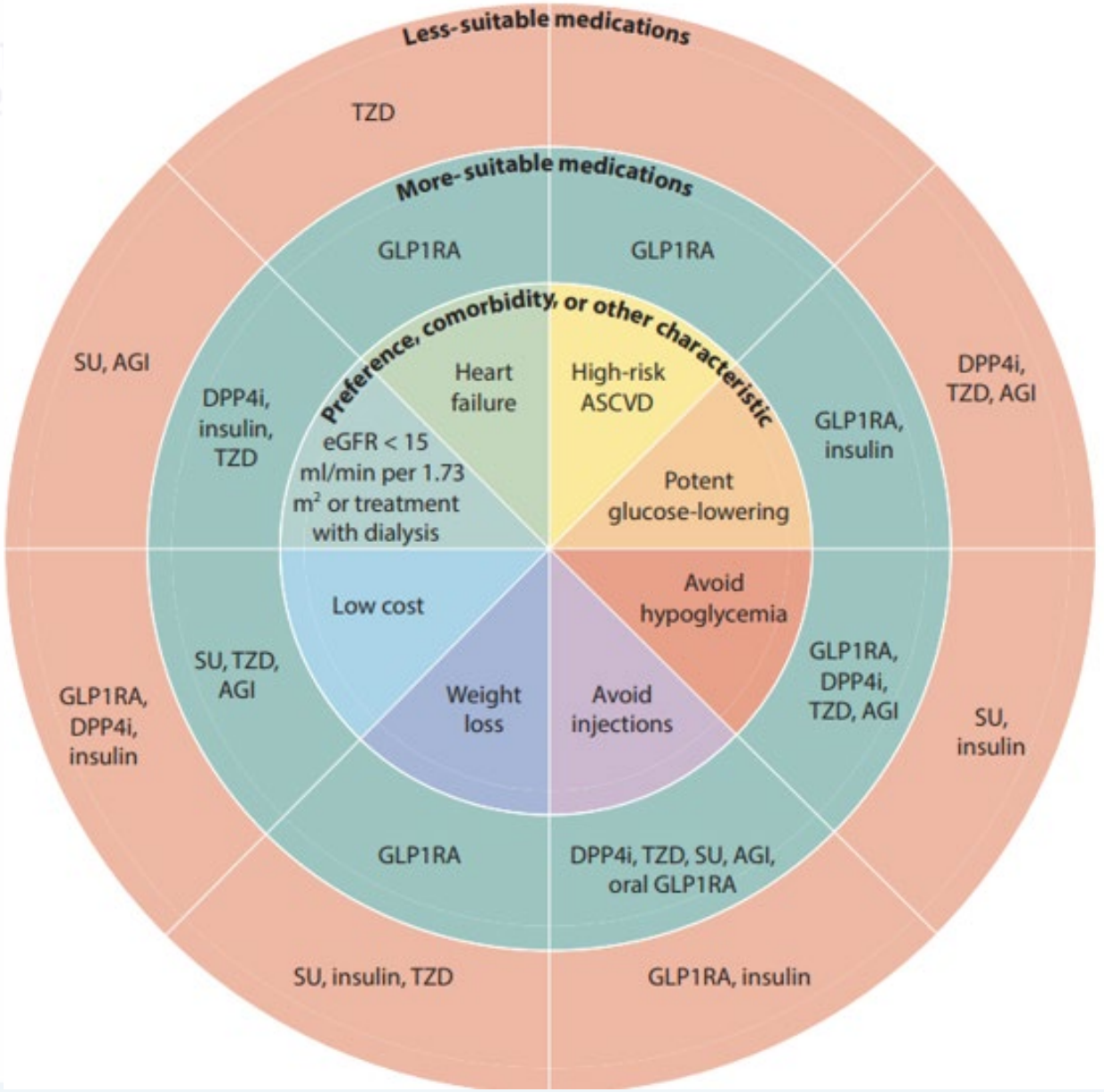


Figure 23 | Treatment algorithm for selecting glucose-lowering drugs for patients with type 2 diabetes (T2D) and chronic kidney disease (CKD). Kidney icon indicates estimated glomerular filtration rate (eGFR; ml/min per 1.73 m^2); dialysis machine icon indicates dialysis. DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium–glucose cotransporter-2; TZD, thiazolidinedione.

Chapter 4: Glucose-lowering therapies in patients with T2D and CKD

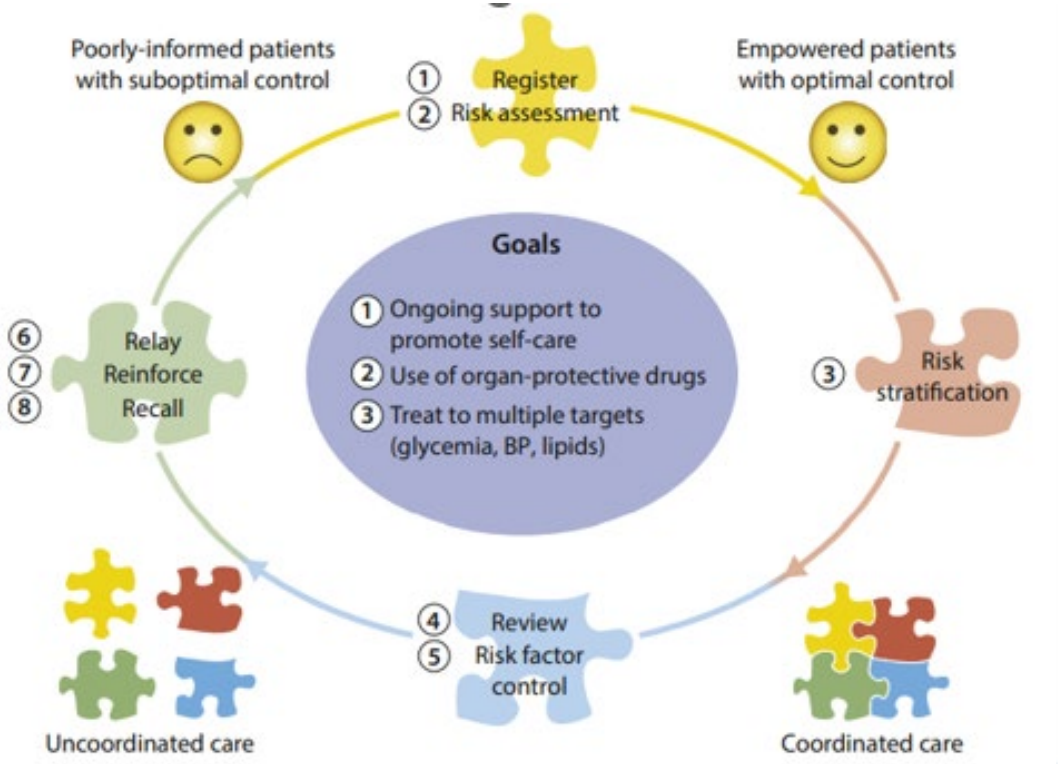
Practice Point 4.3: Patient preferences, comorbidities, eGFR, and cost should guide selection of additional drugs to manage glycemia, when needed, with glucagon-like peptide-1 receptor agonist (GLP-1 RA) generally preferred (Figure 25).



5.2. Team-based integrated care

Recommendation 5.2.1: We suggest that policymakers and institutional decision-makers implement team-based, integrated care focused on risk evaluation and patient empowerment to provide comprehensive care in patients with diabetes and CKD *(2B)*.

Practice Point 5.2.1: Team-based integrated care, supported by decision-makers, should be delivered by physicians and nonphysician personnel (e.g., trained nurses and dieticians, pharmacists, healthcare assistants, community workers, and peer supporters) preferably with knowledge of CKD (Figure 35).



Nuove Terapie

Team Multidisciplinare

L. G.

Life style and self-management

HD

DP

TX

Grazie!

Agata Mollica