Review

Diabetes Mellitus and Chronic Kidney Disease: The Future Is Being Surpassed

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Review

Diabetes Mellitus and Chronic Kidney Disease: The Future Is Being Surpassed

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Abstract

Diabetes mellitus (DM) continuous to be a global world health problem. The Athlas of the International DM Federation for 2023 estimated that 589 million adults (20-79 years) are living with DM and this number could increase to 853 million by 2050. The mortality induced by DM was estimated as up to 3,4 million deaths in 2023. Trends in age-standardized rates of DM-related complications have decreased in the last 15 years; however, a parallel reduction of the incidence of advanced chronic kidney disease (CKD) requiring renal replacement therapy (RRT) has not been observed. Diabetic kidney disease continues to be the first cause of end-stage renal disease worldwide. Until very recently, an integrated approach for the management of the patient with DM and CKD was based on an adequate style of life and nutritional measures associated with a combined treatment of one or various of five classes of drugs: 1) Angiotensin-Converting-Enzyme Inhibitors (ACEI) or Angiotensin II Receptor Blockers (AIIRB). 2) Sodium-glucose-transporter 2 (SGLT2) inhibitors. 3) Glucagon-like peptide-1 receptor agonists (GLP-1 RA). 4). An antagonist of type 1 Endothelin receptor with proved effect to reduce albuminuria and proteinuria. 5) The Mineralocorticoid Receptor antagonist (MRA) Finerenone has been recently tested in RCTs as a renoprotective agent. But, indeed, many new drugs of different therapeutic groups, - many of them proved not to DM management but for the treatment of obesity with or without DM, or HF management -, are now in development and may be added to the five classical pillars described before. These new drugs include other non-steroidal mineralocorticoid receptor antagonists, -Balcinrenone-; aldosterone synthase inhibitors, -Baxdrostat and Vicadrostat-, other GLP1-RA, -Tirzepatide, Survodutide, Retatrutide, Cagrilintide-; other endothelin receptor antagonists,-Zibotentan-; and soluble guanylate cyclase activators,-Avenciguat- . Strategies based on actions on gut microbiota or stem cell therapies will be introduced in the future. The new strategies suggest to combine some of these therapies in adequate personalised doses for an integrated management of patients with DM and CKD. All these measures may ideally be applied in an approach that includes different especialists, patients and health providers, in the context of multidisciplinar teams. Perhaps in the next step we should be able to "fold the curve", to stop the progression to ESRD and the CV

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damage in the patients with DM, allowing definitively to decrease DM as the first cause of advaced CKD.

Keywords: diabetes mellitus; diabetic nephropathy; diabetic kidney disease; chronic kidney disease; obesity; angiotensin II-converting enzyme inhibitors; angiotensin-II-receptor blockers; sodium-glucose-transporter 2-inhibitors; glucagon-like peptide 1 receptor agonists; mineralocorticoid-receptor antagonists; new hypoglycaemic drugs

Introduction

Diabetes mellitus (DM) continuous to be a global world health problem. In November 2024 the global disease burden of DM prevalence and treatment from 1990 to 2022 was published in The Lancet. A pooled analysis of 1108 population representative studies with 141 million participants aged above 18 y.o. estimated that there are 630 million (554–713) people with DM from 1990. The prevalence of DM increased in 131 countries for women and in 155 countries for men. The prevalence of DM is estimated in 828 million (95% CI 757–908) adults for 2040 [1].

On the other hand, the Athlas of the International Diabetes Federation (IDF) for 2023, published in April 2025 [2], estimated that 589 million adults (20-79 years) are living with DM and this number could increase to 853 million by 2050. Three on four adults with DM are living in low and middle income countries. The mortality induced by DM in 2023 was estimated as up to 3,4 million deaths. One trillion USA dollars supposed a 338 % increase in healthy expenditure for DM in the last 15 years. One in eight adults (12,5%) are at high risk of developing T2D and more than 1,8 million children and young adults are living with T1D [2].

These two important studies offer different estimations with regards to the DM prevealence but, in any case, it seems clear that there is a constant increase of the DM prevalence around the world.

As per August 16th 2025, the number of publications related to DM in PubMed.gov is also constantly increasing, achieving 792374 publications. The references to cardiovascular (CV) complications of DM were 382134, 228533 for Diabetic Kidney Disease (DKD) and 112065 for diabetic nephropathy (DN) [3].

Although the standardized rates of DM-related complications, - acute myocardial infarction, stroke or amputations-, have decreased in the last 15 years; a reduction of the incidence of advanced chronic kidney disease (CKD) requiring renal replacement therapy (RRT) has not been achieved. DKD continues to be the first cause of end-stage renal disease (ESRD) worldwide. Data from the ERA registry of 2022, published in 2025 [4] showed that 23% out of the patients with ESKD starting dialysis or requiring a kidney transplant had diabetes as the primary cause of renal disease. The recent data from the REDYT registry, - Registro Español de Diálisis y Trasplante-, of 2023, found that 25,2 % of the patients starting RRT had diabetes as the cause of ESRD [5].

Albuminuria detection or the estimation of glomerular filtration rate (eGFR) has been the classical methods for the diagnostic of CKD, but urinary proteomics analysis are being incorpotared for a better early detection of DKD in individuals with baseline eGFR above 60 mL/min/1.73m2.

In addition, various pannels of serum and urine biomarkers are in development for an early detection of both diseases [6-8].

The clinical picture of the DM patient with advanced CKD has really changed in the last decades, but a very high number of complications are still in progress in these subjects if DM and CKD are not detected in the early stage of both diseases.

Fortunately the multidisciplinary and multifactorial care has effectivelly improved the ancient catastrofic panorama of the patient with DM and progressive CKD.

Integrated approach for the management of the patients with DM and CKD.

The integrated care of the patients is based on five classes of drugs:

1) Angiotensin-Converting-Enzyme Inhibitors (ACEI) and Angiotensin II Receptor Blockers (AIIRB) demonstrated in several studies, - with captopril [9], IRMA II [10] , IDNT [11] with

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irbesartan and RENAAL with losartan [12]-, their beneficial effect regarding reduction of albuminuria and the progression of the renal damage. Thus renin-angiotensin aldosterone system (**RAAS) inhibitors** are maintained as the first step treatment in the DM patient with hypertension and/or albuminuria or proteinuria.(See Table 1).

Table 1. Summary of studies with RAAS Inhibitors, SGLT2 Inhibitors, GLP-1 Receptor Agonists, Endothelin A Receptor Antagonists and Mineralocorticoid Receptor Antagonists.

Name of Study and Authors	Drug	Study Type	N Patients	Patient Type	Results
RAAS Blockers					
Captopril trial, Lewis EJ et el [9]	Captopril vs placebo	Ph III RCT	409 (207 capt, 202 plac)	T1D	50% decrease combined 1EP(x2 sCreat, dialysis,renal transpl).
IRMA II, Parving HH et al [10]	Irbesartan vs plac	Ph III RCT	590	T2D	I End point HR 0,30, p< 0.001
IDNT, Lewis EJ et al [11]	Irbesartan vs amlodipin vs plac	Ph III RCT	1715	T2D	x2 sCreat decrease 21% vs 24% (vs plac p<0.03, vs amlodip < 0.05)
RENAAL, Brenner BM et al [12]	Losartan Vs plac	Ph III RCT	1513	T2D	x2 sCreat decrease 16%(p=0.006), dcase ESRD 28% /(p=0,02), deceae prot[a] 35% (p=0,001)
SGLT2 Inhibitors					
EMPA-REG, Zinman B et al [13]	Empagliflozin vs plac	PhIII RCT	7028 (empa 10 mg N=2345, empa 25 mg (n=2342, plac (n=2333)	T2D	1EP combined decreased 10,5% vs 12,1%, RR 0,86, p<0.001
EMPA REG OTCOME Wanner C et al [14]	Empagliflozin vs plac	PhIII RCT	7028 (empa 10 mg N=2345, empa 25 mg (n=2342, plac (n=2333)	T2D	Incident worsening nephropathy occurred in 12,2% in empag group vs 18,8% in plac goup (HR 0,61 p<0.001). x2 sCreat ocurred in 1,5% vs 2,6% (44% RR reduction). Renal Replacement Therapy was initiated in 0,3% (empa group) vs 0,6% (plac group) (RR 55% reuction).No differences in incident Alb[a].
CREDENCE trial, Mahaffey et al [15]	Canagliflozin vs plac	PhIII RCT	4431 T2D	T2D	1ºEP decrease MACE RR 0,80 (p=0.01), primary EP RR 0,68 (p=0.01) Second EP RR 0.85 (p=0.25). → Decrease MACE and kidney failure
DECLARE, Wiviot SD et al. [16]	Dapagliflozin vs plac	PhIIIRCT	17160 T2D	T2D	MACE reduction HR 0.93 p=0.17, HF reduction 4,9% vs 5,8%, hospitalization HR 0.83, p=0.005. Renal event reduction 4,3 vs 5,6 HR 0.76.

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DECLARE – TIMI, Mosenzon O et al. [17]	Dapagliflozin vs plac.	PhIII RCT	16863 with albuminuria not CKD	T2D	Reduction of Alb[a] and eGFR decline in all categories (p< 0.05).
Toyama et al. [18]	SGLT2 inh. vs plac.	Metaanalysis 27 RCT	7363 T2D + CKD	T2D	1 EP composite renal outomes eGFR decline /dialysis/RTransplant decrease HR 0,71 (29%).
DAPA CKD, Heerspink HJL et al [19]	Dapagliflozin vs plac	PhIII RCT	DM + CKD n=4304. DM= 1455 dapa, 1451 plac.	T2D	1EP composite =or>50% decline eGFR/ESKD/death→ 9,2% in dapagl, 14,5% in plac. RR 0.61, p< 0.001
Zheng Y et al [20]	Syst. Rev. & Metaanalysis (20 qualitative & 9 quantitative studies	RCT	22313 treated with SGLT2 inh. vs plac.	T2D with CKD	Strong evidence for protective therapy for renal health
Natale P et al. [21]	Syst Rev	53 RCT	65241 SGLT2 inh. vs plac.	T2D with CKD	Decreased risk death (2 studies,RR 0,85-0.94). Renal events: decreased RR 0,70-0,89 in 2 studies with 12647 p; decreased RR 0.68-0.78 in 7 studes with 36380 patients.
GLP-1 R Agonists					
STEP 1 to 8 propramme. Bergman NC et al [22]	Review	8 RCT	Semaglutide 2,4 mg sc /week N=1961 pat.	Obesity without DM	At week 68, 14,9% (semagl. group) vs 17,4% (plac group) weight loss.
SURMOUNT-1, Jastreboff et al [23]		2539 p	2539 (1032 with Pre DM)	Obesity	At week 17, 1,3% in tirzepatide group vs 13,3 % in plac group developped T2D, HR 0.12, P< 0.001
Davies MJ et al [24]	Cagrilintide - semaglutide vs plac	1206	Cagrilintide +semag (n=904), placebo (n=342)	Obesity+T2D	At week 68, -13,7% (cagri+semagl) vs - 3,4% (plac) weight loss.
ELIXA Musquiet ME et al [25]	Lixisenatide vs plac	6068 5978 microAlb[a] available	Lixienatide 2250 lixisenatide vs 2191 plac.	T2D	At week 108, % change in Alb[a]: -1,69% in normoAlb[a] (p 0.73); -21,1% in microAlb[a] (p0.05) and –39,18 % in macroprot[a] (p= 0.007)
EXSCEL Holman HH [26]	Exenatide 2 mg/sc/w vs plac		N=14752 (10782 with previous CV disease)	T2D	Primary composite outcome event occurred in 11.4% in the exenatide group and in 12.2% in the placebo group (HR 0.91). Exenatide was noninferior to placebo with respect to safety (P<0.001 for noninferiority) but was not superior to placebo with

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					respect to efficacy (P = 0.06 for superiority). The rates of death from cardiovascular causes, hospitalization for heart failure, and hospitalization for acute coronary síndrome and serious adverse events did not differ significantly between the two groups
LIRA RENAL Davies MJ [27]	Lixienatide vs plac	Ph III RCT	Lixisenatide sc n= 279	T2D + CKD	Weight loss -2.41 kbw vs -1,09 (p< 0.0052). No changes in renal function.
LEADER, Marso SP et al [28]	Liraglutide vs plac	Ph III RCT	N= 94340, Liraglutide (4668) vs plac (n=4672)	T2D	1ºEP comps 13% vs 14,9%, RR 0,87 p< 0.001. Death from CV causes 4,7 vs 6% (RR 0.78, p00.007); deaths from any cause 8,2 vs 9,6 %, RR0.85, p= 0.02
REWIND Gerstain HC et al [29]		PhIII RCT	Dulaglutide 1,5 mg sc/w. Dukagl n) 4949 vs plac (n=4952)	T2D with pevious CV risk factors	1 composite EP 12% vs 13,4 % HR 0,88 p 0.026. No differentcies on mortality rate.
AWARD Tuttle K et al [30]	Dulaglutide vs isuulin glargine	PhIII RCT	Dulaglutide n=577, 1,5 mg sc/w, dulag 0,75 mg sc/w vs insulin glargine	T2D + CKD	At 52 w: eGFR dulaglutide groups : 34 mL/min/1,73m2; eGFR in insulin glargine 31 mL/min/1,73m2 (<0.005). UACR and glucose control without fferences between groups.
FLOW Mahaffy et al [31]	Semaglutide 1 mg sc/week x 52 w	Ph III RCT	N=3533 KDIGO low risk (n=242 p), high risk (n=878 p), very high risk (n=2412)	T2D + CKD	Decrease in CV death/mioc infart c/stroke 18% in tsemaglutide patients, regardless of baseline CKD sever ity.
Endothelin A Receptor antagonists					
SONAR Waijer et al [32]	Atrasentan 1 mg/d vs plac	Ph III RCT	Initial Ph n= 5117; enrichment ph n= 3668 p	T2D + CKD	1EP decrease RH 0.71, highest benefit in patients with higher UACR and lower eGFR . High risk of hospitalization fr HF aceross ll categories of AUCR and eGFR.at baselipne
Mineralocorticoid Receptor Antagonists					
FIDELIO DKD, Bakris G et al [33]	Finerenone vs plac	PhIII RCT	N= 5734, 2833	T2D + CKD	1 EP combined 17,8% vs 21,1% HR 0,86, p0.001; Second EP kidney failure/sustained

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			finerenone, 2841 plac.		decrease eGFR/death renal cause) 13% vs 14,8% HR 0,86 p=0.03
FIGARO Ruilope JM et al [34]	Finernone vs plac	RCT	7352	T2D + CKD	Higher effects on the eGFR decrease <57% cin¡mpsite 1EP HR 0.77 p=0.041, 36% risk reduction for ESRD
FIDELITY Agarwall R et al [35]	Finerenone vs plac	Pool analysis 2 RCT	N=6519 finerenone N=6507 plac	T2D + CKD	Comp 1 EP CV outcome 12,7 % vs 14,4 %, HR0.86, p=0.00018. Composite kdney outcomes: 5,5% vs 7,1%, HR 077, p=0.0002
Agarwall R et al [36]	Finerenone 10 mg/d, empagliflozin 10 mg/d, or combined finerenone + empagliflozin	PhIII RCT	Finerenone n= 258 p; empagliflozin n=261 p, combined t n=265 p	T2D + CKD	At day 180, the reduction in the UATC ratio with combination therapy was 29% greater than that with finerenone alone (HR 0.71; P<0.001) and 32% greater than that with empagliflozin alone (0.68; P<0.001

RAAS= Renin Angiotensin II Aldosterone System. SGLT2 I= Sodium glucose transporter inhibitor. GLP-1RA= Glucagon-like peptide 1 agonist. Ph= Phase. RCT= Randomised Clinical Trial. T2D= Type 2 diabetes. CKD= chronic kidney disease. 1EP= Primary End Point. 2EP= Secondary End point. ERSD= End Stage Renal Disease.HR= Hazard Ratio. RR= RelativeRisk. UACR= Urine Albumin to Creatine Ratio. eGFR= estimared Glomerular Filtration Rate.

2) **Sodium-glucose-transporter 2 (SGLT2**) inhibitors has efficiently been added to the usual antidiabetic therapy for an adequate metabolic control in subjects with DM but also showing a safe CV and nephro protective profile. The studies of Zinman B et al [13] and Wanner C et al [14] with empagliflozin, the CREDENCE trial with canagliflozin [15], the DECLARE and DECLARE-TIMI studies with dapagliflozin [16,17] and many others afterwards have showed the benefits for an optimal hypoglycaemic management in addition to CV and renal protection.

A meta-analysis of Toyama et al [18] recruited data from 27 studies with SGLT2 inhibitors. In 7363 patients with T2DM and CKD, SGLT2 inhibitors lowered glycated haemoglobin as well as blood pressure, body weight and albuminuria. A reduction of the risk of CV death, nonfatal myocardial infarction or nonfatal stroke and heart failure (HF) was also observed, without a clear effect on all-cause mortality. The study showed an attenuation of the annual decline in the eGFR slope and also a significant risk reduction of the composite renal outcome (HR, 0.71; 95% CI, 0.53-0.95).

Heerspink HJL et al [19] studied, in a randomized clinical trial (RCT), the effect of dapagliflozin in 4304 patients with CKD with or without DM, with an eGFR of 25 to 75 mL / min/ 1.73 m^2 and a urinary albumin-to-creatinine ratio (UACR) of 200 to 5000 mg/g. These patients received dapagliflozin (10 mg once daily) or placebo. After a median follow-up of 2.4 years, a primary outcome event of a composite of a sustained decline in the eGFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes occurred in ~~197 (~~9.2%~~)~~ of patients (n=2152) in the dapagliflozin group and ~~312 (~~14.5%~~)~~ of patients (n=2152) in the placebo group (HR, 0.61; relative risk reduction, 39%; P<0.001).The specific renal end-point was reduced by 44% (P<0.001), and a composite of death from CV causes or hospitalization for HF was reduced by 29% (P = 0.009). ~~One hundred and one participants (~~4.7% ~~)~~ of patients died in the dapagliflozin group and 146 ~~participants (~~ 6.8% ~~)~~ ~~died~~ in the placebo group (HR, 0.69; P = 0.004), resulting in a 31% relative risk reduction in all-cause mortality. The effects of dapagliflozin were similar in patients with or without DM . Interestingly, new studies are continuously been incorporated on the long-term effects of SGLT2 inhibitors [20,21). (See Table 2).

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Table 2. Summary of some studies with new emerging molecules for the treatment of patients with DM and/or Obesity and /or Chronic Kidney Disease.

Name of study and authors	Drug	Study type	N patients	Patient type	Results
Mineralocoticoid Receptor Antagonists					
MIRACLE, Lam CSP et al [41]	Balcinrenone (10,50 or 150 mg/d) + Dapagliflozin 10 mg/d Vs Dapag 10 g/d + plac.	PhII RCT	166 planned, not achieved	CKD + symptomatic HF	-Stopped early because of low recruitment. -No specific response relationship dose-dependent incrases in s K. - No UACR decrease t 12 weeks.
Aldosterone-Synthase Inhibitors					
Freeman MW et al [42]	Baldrostat 10 mg/d by 7 days	Ph I pharmacokinetic study	N= 32	CDK diverse degrees	Renal impairment had no significant impact on systemic exposure or clearance of baxdrostat. Dose adjustment due to PK differences in patients with kidney disease is probably not necessary.
EASi KIDNEY, Judge PK et al [43]	Vicadrostat 10 mg/d (+ RAAS inh + empagliflozin 10 mg/d) vs plac	Ph III Runnning st.	Stratum 1: 4800 p. Stratum 2; 6200 p. Follow-up 3 y.	CKD	1070 outcomes are expected in 3 years in each group.. 1 EP:composite kidney progression and 2EP Composite CV death/HF hospitalization
GLP-1 R Agonists					
Garg SK et al [44]	Tirzepatide vs controls	Retrospective Ph IV	T1D n=84 Controls n= 38	T1D + BMI =or> 27 kbw/1,73 m2	Tirzepatide treated patients significantly losed more weight (-59 ± 4.6 lbs [-23.4%]) compared with a

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					gain of (+1.7 ± 5.0 lbs [+1.8%]) in controls over 21 months. The HbA1c decreased more in group than controls (-0.50 ± 0.07% and -0.24 ± 0.09%, respectively, *P* = 0.017).Tirzepatide significantly improved total and low-density lipoprotein cholesterol, triglycerides, systolic blood pressure, and eGFR. The eGFR declined significantly in controls but not in the tirzepatide users
Le Roux et al [45]	Survodutide Sc 0,6/2,4/3,6/4,8 mg/w, dose escalating Vs plac	Ph II	N= 387	Overweight or obesity	In people with a BMI ≥27 kg/m², survodutide significantly reduced body weight and waist circumference when compared with placebo, in prespecified subgroups based on sex and baseline BMI, and was tolerated at all doses tested.
Ma et al [46]	10 nmol/kbw intraperitoneal injection of Liraglutide vs Tirzepatide vs Retatrutide	Experimental T2D model	10 Db/db mouse Per group	Experimental db/db mouse	Retatrutide demonstrated superior effectiveness in reducing weight and improving renal function in db/db mice compared to Liraglutide and Tirzepatide. it markedly

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					suppressed the expression of pro-inflammatory cytokines (TNF-α, caspase-1, and NLRP3) and pro-fibrotic factors (fibronectin, α-SMA, and collagen I) in the kidneys of mice. Retatrutide enhanced liver function, reduced triglyceride levels, cholesterol levels, low-density lipoprotein cholesterol, elevated high-density lipoprotein cholesterol, and increased the content of intestinal metabolite butyrate in db/db mice when compared to the other two drugs., Tirzepatide exhibited better effects on lowering blood glucose, weight loss, lipid reduction, and improvement of DKD compared to Liraglutide.
Endothelin A Receptor Antagonists					
ZENITH-CKD Heerspink HJL et al [47]	-Zibozentan 1,5 mg/d + Dapagliflozin 10 mg/d; -Zibot 0,25 mg/d +	PhIIb RCT	CKD (n= 449 zibot 1,5 + dapa); n=91 zibot 0.25 + dapa) N=177 dapa + plac	CKD	At 12 w: UACR decrease -33,7% ($p<0.001$, in zibot 1,5 mg group); -27% ($p=0.0022$) in zibot 0.25 group,

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	dapaglif 10 mg/d; -Dapagliflozin 10 mg/d + plac.				all groups vs dapa + plac. Fluid retention: 18% in zibot 1,5 mg; 9% in zibot 0,25 mg; 8% in dapa + plac.
Guanylate cyclase activators					
Heerspink JHL et al [48]	Avenciguat 1,2 or 3 mg/TID vs plac.	PhIII RCT, studies 1 and 2 Pooled analysis	500 CKD patients, from whom DM=243 in study 1 and 27 in study 2.	CKD or CKD+T2D.	UACR in 10 h urine: decrease 15,5%(avenciguat 1mg), -13,2% (avenciguat 2mg) and -21,5% (avenciguat 3 mg)- UACR in first morning void urine: -19,4% (avenciguat 1mg), -15,5% (avenciguat 2 mg) and -21,4% (avenciguat 3 mg)

DM= Diabetes Mellitus. CKD= Chronic Kidney Disease. HF= Heart Failure. Ph= phase. RCT= Randomised Clinical Trial. UACR= urine Albumine to creatinine ratio.eGFR= estimared Glomerular Filtration Rate. CV= cardiovascular. y = years. T1D= Type 1 Diabetes. T2D= Type 2 diabetes. BMI= Body Mass Index. TID= three times per day.

3) **Glucagon-like peptide-1 receptor agonists (GLP-1 RA)** can improve CV and renal events in DKD. These antidiabetic drugs can be safetly used without an increased risk of hypoglycemia in various CKD stages, in patients with an eGFR above 15 mL/min/1.73 m2. These agents have demonstrated to prevent the onset of albuminuria and to retard the decline of GFR in patients with DM, allowing weight reduction and CV benefits. The effects on body weight sustain these drugs as a solid therapy against obesity [22, 23, 24]. Currently the GLP1R agonists are only recommended in Type2 DM.

A variety of RCT with GLP1-RA showed positive results in the prevention of new onset proteinuria [25-30] (See tabla 1).

Most recently in the FLOW study with 1 mg weekly subcutaneous semaglutide [31], 3533 participants with T2D, with a median follow-up of 3.4 years were randomized. Low or moderate KDIGO risk was present in 6.8% , while 24.9% had high and 68.3% had very high KDIGO risk. Semaglutide reduced CV death, MI and stroke by 18% 0.82 (P = .03) with consistency across eGFR categories, UACR levels, and KDIGO risk classification (all P-interaction > 0.13). Death due to any cause was reduced by 20% (HR 0.80 P = .01) , with consistency across eGFR and KDIGO risk class (P-0.21 and 0.23). The P-interaction treatment effect for death due to any cause by UACR was .01 [<300 mg/g HR 1.17; ≥300 mg/g HR 0.70.

4). The **antagonist of type 1 Endothelin receptor** atrasentan has proved to reduce albuminuria and proteinuria. Atrasentan can decrease the risk of kidney failure but at the expenses to increase edema and HF. Proteinuria can be reduced in patients with severe CKD, but the risk of HF may be increased. The effects of atrasentan on kidney and HF events according to baseline eGFR and UACR

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in a *post hoc* analysis of the Study of Diabetic Nephropathy with Atrasentan (SONAR) trial have been analysed byWaijer SW et al [32]. They studied the effect of atrasentan versus placebo in 3668 patients with T2D and CKD with elevated albuminuria. Atrasentan reduced the ~~relative risk~~ RR of the primary kidney outcome, - renal composite, HF hospitalization (HR, 0.71)-, consistently across all subgroups of baseline eGFR and UACR (*P* >0.21). Patients in the highest UACR and lowest eGFR subgroups obtained the maximal benefit (p<0.01). The risk of HF hospitalization was higher in the atrasentan group (HR 1.39).

5) Finerenone, a non-steroidal **Mineralocorticoid Receptor antagonist (MRA),** has been tested in RCTs as renoprotective agent. The phase III studies FIDELIO-DKD [33] and FIGARO-DKD [34], and the pooled analysis FIDELITY [35] in patients with T2D and CKD examined CV and kidney outcomes in different stages of CKD. Among 13.026 patients with a median follow-up of 3.0 years the composite CV outcome occurred in 12.7% of the patients receiving finerenone and 14.4% ~~(n=939) of the patients~~ in the placebo group ┤ (HR, 0.86; P = 0.0018) ├. The composite kidney outcome occurred in 5.5% of patients treated with finerenone and 7.1% ~~(n=465)~~ receiving placebo (HR, 0.77; P = 0.0002), 23% RR ~~relative risk~~ reduction. Hyperkalaemia as the cause of treatment discontinuation was more frequently observed in patients receiving finerenone (1.7%) than placebo (0.6%).

Ruilope LM et al [34], in a post-hoc analysis of FIGARO-DKD, observed that finerenone reduced the risk of CV events in patients with T2D and stage 3 CKD. FIGARO-DKD included patients with UACR 30 to <300 mg/g and eGFR 25 to 90 mL/min/1.73 m2 or UACR 300 to 5000 mg/g and eGFR ≥60 mL/min/1.73 m2. A decrease >40% in the eGFR was observed in a lower rate with finerenone compared with placebo (HR= 0.87; P = .069). The treatment with finerenone was associated with a RR of 23% (HR 0.77 (p=0.041), if an eGFR reduction > 57% was considered. These RCT did not included any parameter or biomarker to evaluate the effect on fibrosis. In patients with severely increased albuminuria, a more intense effect of finerenone was observed. Improvements in UACR, eGFR slope and CV risk were evident in both subgroups with finerenone.

In a very recent study, Agarwal R et al [36] have analysed the effect of finerenone (10 or 20 mg/day) (N=264), empagliflozin (10 mg/day, N=267) or the combination of the two drugs in a RCT in patients with eGFR 30 to 90 mL/min/1,73m2-, UACR of 100 to = or < 5000mg/g and T2D. The initial combination with finerenone- empagliflozin led to a greater reduction in the UACR than either treatment alone.

Patients with DM and CKD are in very high risk to develop kidney failure, atherosclerotic CV disease, HF, and premature death.

The Kidney Disease Improving Global Outcomes (KDIGO) 2022 [37] and the 2022 American Diabetes Association (ADA) Standards of Medical Care in Diabetes and the Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease [38] have added evidence-based recommendations. The new ADA 2025 Guidelines for the standard care of DM [39] insists in some aspects that should be taken into consideration when comparing to the Guidelines of 2024: 1) Diagnostic may consider antibody-based screening for presymptomatic T1D in individuals with a family history of the disease. 2) GLP-1 RA or dual GIP-GLP1 RA are recommended for their multifaceted benefits in diabetes management. 3) The adequate water consumption, a high-quality and sustainable eating patterns such as plant-based diet and a recommendation to replace sugar with non-nutritive sweeteners in moderation and short-term to facilitate caloric restriction may be offered as a Dietary guidance . 4) Digital Technology powered by the systems or a Continuous Glucose Monitoring (CGM) for individuals with T2D on non-insulin regimens as well as those on insulin may be implemented.

New emerging molecules for the management of patients with CKD and/or DM and /or obesity (See Table 2).

While our thoughts were yet installed into the future for the management of patients with DM and DKD [40], the future is being constantly surpassed. Many new drugs of different therapeutic groups are now in development and may be added to the five classical pillars described before, but also for the treatment of patients with CKD without DM. Numerous RCTs are currently in

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progress and will offer surprising results in the next months and years. These new drugs include other non-steroidal mineralocorticoid receptor antagonists, such as Balcinrenone [41]; aldosterone synthase inhibitors, such as Baxdrostat [42] and Vicadrostat [43]; different GLP1-RA such as Tirzepatide [44], Survodutide [45], Retatrutide [46]; new endothelin receptor antagonists, such as Zibotentan [47] and soluble guanylate cyclase activators, such as Avenciguat [48].

Many patients with HF have CKD and may not tolerate MRA. Lam CSP et al. investigated the efficacy and safety of the mineralocorticoid receptor modulator **balcinrenone** in combination with dapagliflozin in a phase 2 study [41].

From January 2021 to October 2023, 133 adults with symptomatic HF, ejection fraction < 60%, eGFR ≥ 30 to ≤ 60mL/min/1.73 m2 and UACR ≥ 30 to < 3000 mg/g, were randomized to receive balcinrenone 15, 50 or 150 mg/day plus dapagliflozin 10 mg/day, or dapagliflozin 10 mg/day plus placebo, for 12 weeks. Enrolment was stopped early because of slow recruitment. Relative reductions in UACR from baseline to week 12 (primary endpoint) were not significantly different between the balcinrenone plus dapagliflozin groups versus dapagliflozin plus placebo. There was no clear balcinrenone dose-response relationship. Possible dose-dependent increases in serum potassium levels, reduced eGFR in the highest dose group, and non-significant trends towards reduced N-terminal pro-B-type natriuretic peptide levels were observed. Hyperkalaemia led to discontinuation in two participants treated with balcinrenone plus dapagliflozin and none in those receiving dapagliflozin plus placebo. The study did not showed significant reduction in UACR probably due to the small sample size [41]

Baxdrostat is a selective small-molecule aldosterone synthase inhibitor in development to treat hypertension and CKD. In a phase 1, open-label, parallel-group study [42] the safety and pharmacokinetics (PK) of baxdrostat was assessed in participants with varying degrees of renal function. Three groups of individuals were included into the study: controls (eGFR ≥ 60mL/min/1,73m2), patients with moderate to severe renal impairment (eGFR 15-59 mL/min/1,73m2), or with stage 5 CKD (eGFR < 15mL/min/1,73 m2) and received a single 10-mg baxdrostat dose. Pharmacokinetic blood and urine samples were analyzed at 7 days. Thirty-two participants completed the study. Any patient died and only one mild diarrhea adverse event was registered. No clinically significant changes in laboratory parameters, vital signs, physical examinations, or ECGs were observed. Plasma concentration-time curves of baxdrostat were similar among all groups. Urine PK parameters (12% excreted) in the moderate to severe renal impairment and control groups were similar. Minimal urinary baxdrostat excretion was reported in te renal failure group. . Renal impairment had no significant impact on systemic exposure or clearance of baxdrostat. This fact suggests that dose adjustment due to PK differences in patients with kidney disease is probably not necessary.

A Phase II study in 586 patients with albuminuric CKD have shown that 10 mg of **vicadrostat** (BI690517) [43], another aldosterone synthase inhibitor, reduced UACR by 40% compared with placebo, with or without associated empagliflozin treatment. It use added to an SGLT2i may decrease the risk of hyperkalemia, improving tolerability, and allowing to treat more patients, including those with higher levels of blood potassium. This approach will be tested in the EASi-KIDNEY (NCT06531824), a phase 3 double-blind placebo-controlled trial by assessing the safety and cardiorenal efficacy of vicadrostat in combination with empagliflozin in 11000 patients with CKD and with or without diabetes.

CVD and DKD biomarkers with off-label long-term (21 months) use of **tirzepatide** in over weighed (OW) or obese (OB) adults with T1D were evaluated in a retrospective chart review study (44), and data from 84 OW/OB adults with T1D who received tirzepatide since July 2022 and treated for a minimim of 6 months were analysed. A control group (n = 38) was matched for age, DM duration, sex, glycosylated hemoglobin (HbA1c), and body mass index (BMI). Data were collected electronically over 21 months of treatment. eGFR over time Linear mixed effects models were used to examine the changes in lipids and blood pressure. Tirzepatide users had a slightly higher

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baseline BMI than controls, 35.2 ± 4.8 kg/m2 and 33.3 ± 4.2 kg/m2 (P = 0.03), respectively. Lost of weight (-59 ± 4.6 lbs [-23.4%]) was higher in the tirzepatide treated group compared with a gain (+1.7 ± 5.0lbs [+1.8%]) in controls. The HbA1c decreased more in patients using tirzepatide than in controls (-0.50 ± 0.07% and -0.24 ± 0.09%, respectively, P = 0.017). Tirzepatide treated patients significantly improved triglycerides, total and low-density lipoprotein cholesterol, systolic blood pressure, and eGFR, changes that remained significant after adjusting for weight and HbA1c. The eGFR declined significantly in controls but not in the tirzepatide group. The authors concluded that long-term use of tirzepatide in OW/OB adults with T1DM results in more than 23% weight loss and sustained improvement in glucose control. A significant improvement in cardiovascular biomarkers and preservation of kidney function was observed, independently of changes in weight and/or HbA1c. Nevertheless we must say that currently tirzepatide has no indication in T1D.

The efficacy and safety of **survodutide,** a GLP1 dual Receptor agonist, in people with a BMI ≥ 27 kg/m2 was tested in 387 individuals (aged 18-75 years, BMI ≥27 kg/m2, without DM and with no CKD) who were randomized 1:1:1:1:1 to once-weekly subcutaneous survodutide (0.6, 2.4, 3.6 or 4.8 mg) or placebo for 46 weeks (20-week dose escalation; 26-week dose maintenance). Patients were categorized according to sex and baseline BMI. Data were analysed descriptively in accordance to the dose assigned at randomization using on-treatment data or all data censored for COVID-19-related treatment discontinuation. (ClinicalTrials.gov number: NCT04667377). After 46 weeks treatment, females had greater reductions in body weight and waist circumference than males. Participants with a lower baseline BMI had greater proportional reductions in body weight than those with a higher baseline BMI. The trend was reversed for reductions in waist circumference. Rates of adverse events were comparable between subgroups for sex and baseline BMI. The most frequently reported gastrointestinal effect was nausea in all subgroups [45].

With regards to a new GLP1 RA, a study was conducted in db/db mice, **an** experimental model of T2D, to assess and compare the therapeutic efficacy of Liraglutide, Tirzepatide, and **Retatrutide** in treating DKD [46]. Experimental animals were administered intraperitoneal injections of Liraglutide (10 nmol/kg), Tirzepatide (10 nmol/kg), and Retatrutide (10 nmol/kg) for 10 weeks. The effectiveness of these three drugs in controlling blood glucose levels, reducing weight, and improving serum biochemical indicators and DKD was tested. Renal inflammation and fibrosis indexes were measured and compared. The content of intestinal metabolite butyrate was compared to reflect the regulatory effects of these three drugs on gut microbiota.

Retatrutide demonstrated superior effectiveness in reducing weight and improving renal function in db/db mice compared to Liraglutide and Tirzepatide. The expression of pro-inflammatory cytokines (TNF-α, caspase-1, and NLRP3) and pro-fibrotic factors (fibronectin, α-SMA, and collagen I) was signifficantly suppressed in the kidneys of mice. Retatrutide substantially enhanced liver function, reduced triglyceride and cholesterol levels, low-density lipoprotein cholesterol, elevated high-density lipoprotein cholesterol, and increased the content of intestinal metabolite butyrate when compared to the other two drugs. But despite its ability to lower blood glucose levels, Retatrutide was not superior for the blood glucose control. Tirzepatide showed better effects on lowering blood glucose, weight loss, lipid reduction, and improvement of DKD compared to Liraglutide. The authors concluded that Retatrutide and Tirzepatide were significantly effective in improving DKD, controlling blood glucose and body weight. Retatrutide was the most effective in improving DKD and body weight, while Tirzepatide was the most effective in controlling blood glucose. The reason to include in our review the results of an animal experimental study comparing the effects of these drugs , lies on the benefits of these agents on renal and liver funtion, that could probably be applied to the human beings in subsequent RCT.

In the same way we wish to include some studies with regards to obesity, due to its frequent association with T2D and CKD and its impact on cadiovascular and kidney complications.

Heerspink HLJ et al [47] have conducted a double-blind, active-controlled, Phase 2b study to evaluate the efficacy and safety of the endothelin A receptor antagonist **zibotentan** in combination with the SGLT2 inhibitor dapagliflozin in 415 adults with CKD (Zibotentan and Dapagliflozin for the

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Treatment of CKD; ZENITH-CKD). Participants are being randomized (1:2:2) to zibotentan 0.25 mg plus dapagliflozin 10 mg once daily, zibotentan 1.5 mg plus dapagliflozin 10 mg and dapagliflozin 10 mg alone, for 12 weeks followed by a 2-week off-treatment wash-out period. The primary endpoint is the change in log-transformed UACR from baseline to week 12. Secondary objectives include change in blood pressure from baseline to week 12 and change in eGFR. Other defined events will include changes in weight gain or B-type natriuretic peptide levels. At baseline 447 patients were randomized and received treatment in placebo/dapagliflozin (n = 177), zibotentan 0.25 mg/dapagliflozin (n = 91) and zibotentan 1.5 mg/dapagliflozin (n = 179). The mean age was 62.8 years, 30.9% were female and 68.2% were white. The mean baseline eGFR of patients was 46.7 mL/min/1.73 m² and the geometric mean UACR was 538.3 mg/g. This study will evaluate the UACR-lowering efficacy and safety of zibotentan with dapagliflozin as a new treatment for CKD.

At 12 week, UACR decrease -33,7% (p<0.001, in zibotentan 1,5 mg group); -27% (p=0.0022) in zibotentan 0.25 group, all groups vs dapagliflozin plus placebo. The percentage of fluid retention was 18% in zibotentan 1,5 mg treated patients, 9% in zibotentan 0,25 mg and 8% in dapagliflozin plus placebo. This study is continuing in a Phase III trial to test the dose efficacy and safety for a long term follow-up.

Avenciguat is a novel, potent soluble guanylate cyclase activator in development for CKD. Two trials investigated avenciguat in diabetic (NCT04750577) and non-diabetic (NCT04736628) CKD. A prespecified pooled analysis of two randomized, double-blind, placebo-controlled trials [48] have included adults with CKD (eGFR ≥ 20 and < 90 mL/min/1.73 m2 and UACR ≥ 200 and < 3500 mg/g). The patients were randomized to 20 weeks of placebo or avenciguat 1, 2, or 3mg three times daily (TID), associated to ACEI or AIIRB. The primary end point was change from baseline in UACR in 10-hour urine at week 20. The secondary end point was UACR change from baseline in first morning void urine (FMVU) at week 20. Five hundred patients (mean age 62 +/- 13 years; mean eGFR 44 +/- 18 mL/min/1.73 m² and median 10-hour UACR 719 [379–1285] mg/g were treated with avenciguat 1 mg (n=125), 2 mg (n=126), or 3 mg (n=127) `presentor placebo (n=122). DM affected all 243 patients in the frst study and 27 of 261 patients in the second. Avenciguat 1, 2, and 3 mg reduced UACR in 10-hour and FMVU versus placebo throughout the treatment period. At week 20, placebo-corrected geometric mean changes (95% C.I.) from baseline in UACR in 10-hour urine with avenciguat 1, 2, and 3 mg were −15.5% (−26.4 to −3.0), −13.2% (−24.6 to −0.1), and −21.5% (−31.7 to −9.8), respectively. Corresponding changes in FMVU were −19.4% (−30.0 to −7.3), −15.5% (−26.9 to −2.5), and −23.4% (−33.5 to−11.8), respectively. The overall frequency of adverse events was low and similar to placebo. The number of patients who discontinued the study drug due to adverse events with avenciguat 1, 2, and 3 mg TID were five (4%), 11 (9%), and 11 (9%), respectively, compared with four (3%) in the placebo group.

New potential horizons for the treatment of DKD and also of CKD without DM , such as strategies based on actions on gut microbiota or stem cell therapies are expected in a no longer time.

In conlusion: Additionally to the aplication of the standards for the management and the clinical practice guidelines, the combination of some new molecules in adequate personalised doses offers a better way for an integrated management of patients with DM and CKD. The approach that includes different especialists, patients and health providers, working in multidisciplinar teams and affording educational programmes may be based on an early diagnostic of both DM and CKD. An optimal time to refer the patient with DM and renal involvement to nephrology care should be the key point to coordinate the integrated multifactorial management of our patients [49]. Perhaps in a next step we should be able to “fold the curve”, to slow the progression to ESRD and the CV damage in the patients with DM, allowing definitively to decrease DM as the first cause of advaced CKD.

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