Nonsteroidal MRAs as part of the comprehensive approach to CKD: Guideline updates

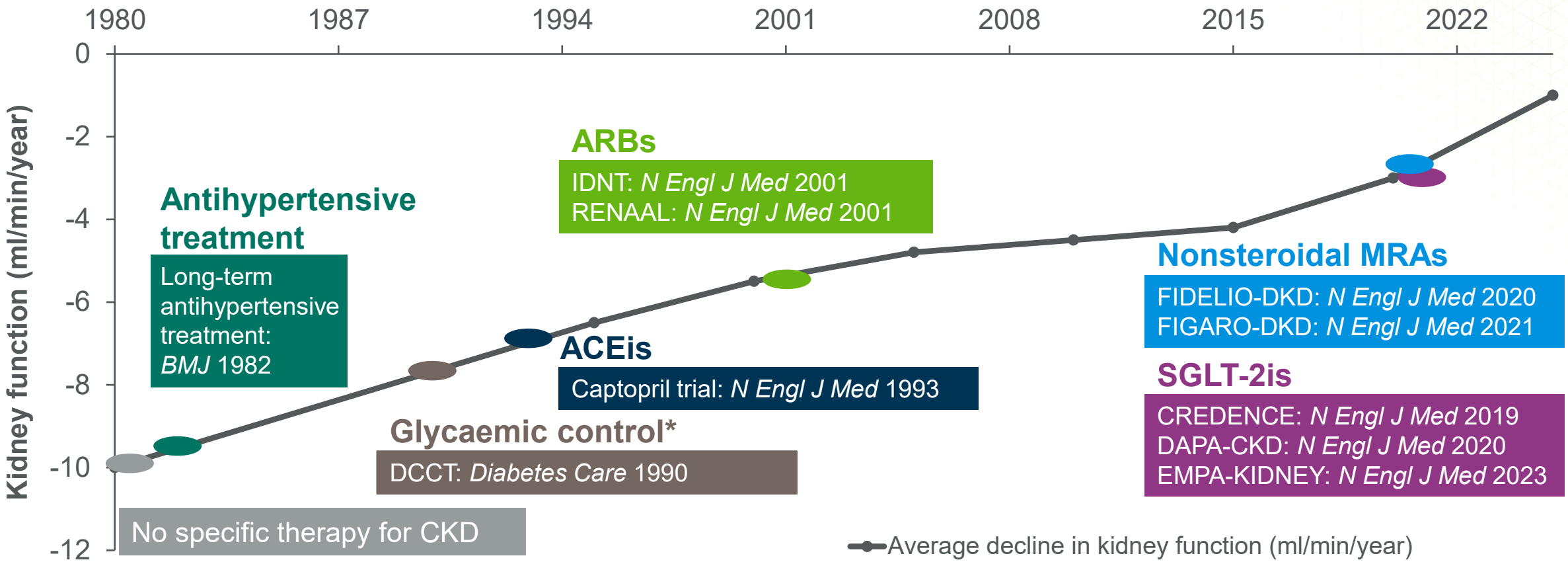
Beatriz Fernández-Fernández

Servicio de Nefrología e Hipertensión,
Hospital Universitario Fundación Jiménez Díaz

Madrid, Spain

Date of preparation: June 2023
MA-M_FIN-ALL-1232-1, MA-M_FIN-IT-0074-1
Bayer sponsored symposium

Therapies to reduce CV risk and slow CKD progression associated with T2D have evolved over the past 40 years



Recent findings on the cardiorenal benefits of finerenone and SGLT-2is have changed the therapeutic landscape for CKD and T2D

*Microvascular complications

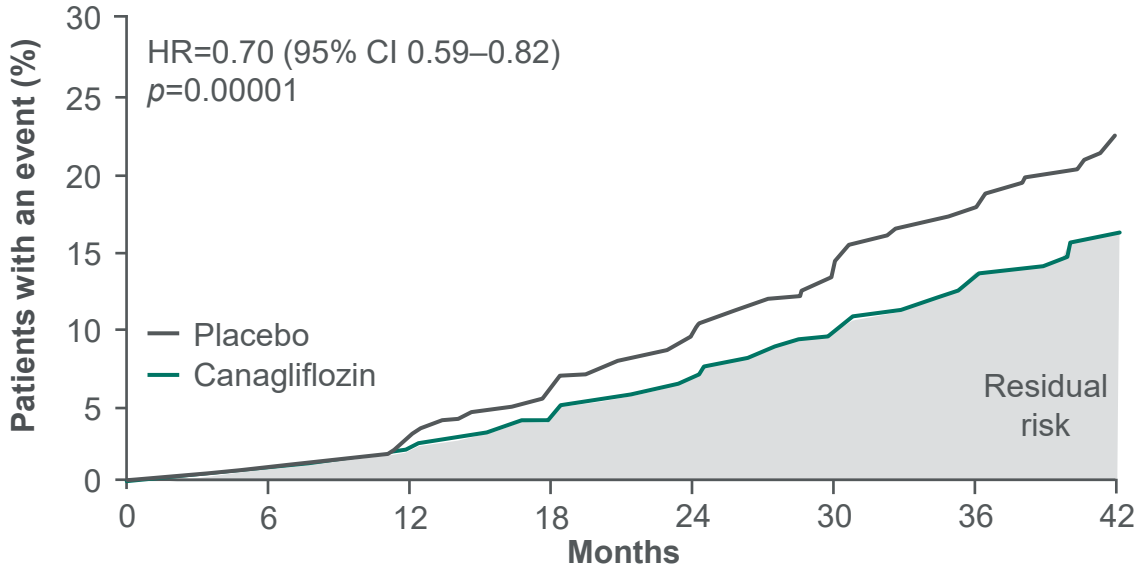
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; SGLT-2i, sodium-glucose co-transporter-2 inhibitor

Adapted from Naaman SC & Bakris GL. In: Chronic Kidney Disease and Type 2 Diabetes. Arlington: American Diabetes Association; 2021. p28–32

Please refer to slide notes for individual trial references

Despite RAAS blockade and SGLT-2 inhibition, patients with T2D and advanced CKD remain at risk of CKD progression

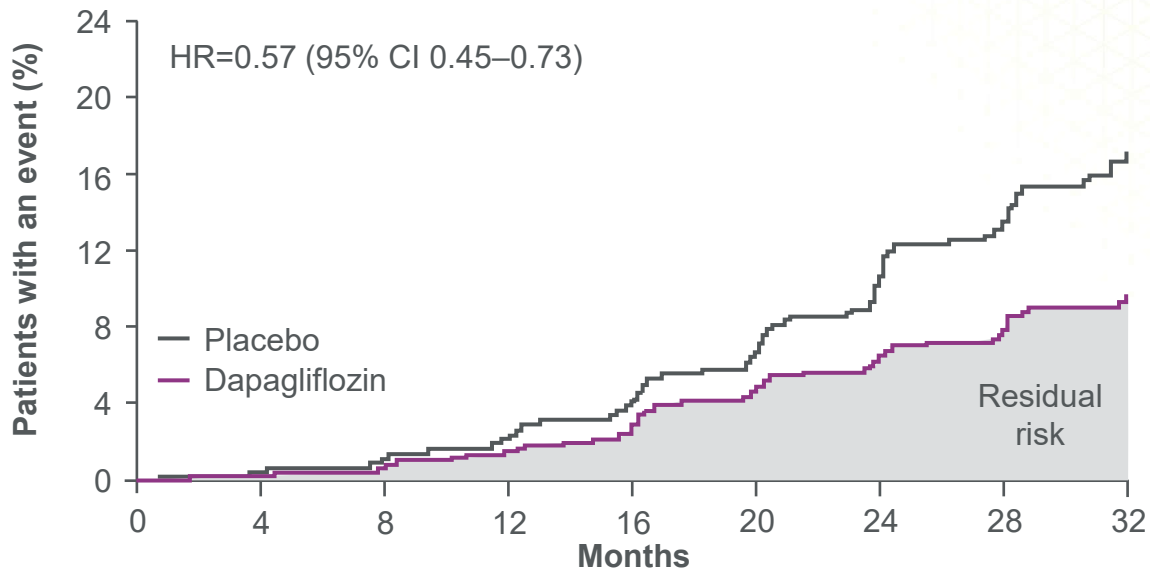
CREDENCE: Canagliflozin (+ ACEi/ARB) vs placebo[1]



Patients with moderately increased albuminuria: 11%
Patients with severely increased albuminuria: 88%
Median UACR: 927 mg/g

Primary composite outcome:
Kidney failure, doubling of SCr or death from kidney/CV causes

DAPA-CKD: Dapagliflozin (+ACEi/ARB) vs placebo (T2D subgroup)[2]



Patients with severely increased albuminuria: 89.7%
Median UACR: 949 mg/g

Secondary composite renal outcome:
Sustained ≥50% eGFR decline, ESKD or renal death

CI, confidence interval; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HR, hazard ratio; UACR, urine albumin-to-creatinine ratio; RAAS, renin-angiotensin-aldosterone system; SCr, serum creatinine

1. Perkovic V, *et al*. *N Engl J Med* 2019;380:2295–2306; 2. Wheeler DC, *et al*. *Lancet Diabetes Endocrinol* 2021;9:22–31

Finerenone is a first-in-class nonsteroidal MRA with clinically proven kidney and CV benefits[1–5]

Almost 1 million molecules screened

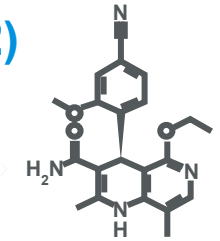
Molecules **identified and refined**

Finerenone identified

Finerenone **tested**

Finerenone (BAY 94-8862)

A **nonsteroidal MRA** with **high selectivity and potency** for the MR



In phase III studies, finerenone showed CV and kidney benefits in patients with CKD and T2D treated with a maximum tolerated dose of RASi[4,5]

FIGARO-DKD[4] FIDELIO-DKD[5]

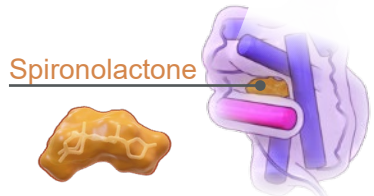
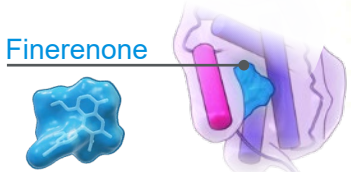
MR, mineralocorticoid receptor; RASi, renin–angiotensin system inhibitor

1. Kim DL *et al. Endocrinol Metab (Seoul)* 2023;38:43–55; 2. Bärfacker L, *et al. ChemMedChem* 2012;7:1385–1403; 3. Fagart J, *et al. J Biol Chem* 2010;285:29932–29940; 4. Pitt B, *et al. N Engl J Med* 2021;385:2252–2263; 5. Bakris GL, *et al. N Engl J Med* 2020;383:2219–2229

Finerenone and steroidal MRAs have key pharmacodynamic and pharmacokinetic differences[1–3]

Pre-clinical data

Clinical data

	Aldosterone antagonists		Finerenone
			
Structural properties	Flat (steroidal)	Flat (steroidal)	Bulky (nonsteroidal)
Potency against MR	+++	+	+++
Selectivity for MR	+	++	+++
CNS penetration	+	+	–
Half-life	>20 hours*	4–6 hours*	2–3 hours#
Active metabolites	++	–	–
Breast-related side effects	++	(+)	–
Effect on BP	+++	++	+
Indication (SmPC)	**Congestive HF[4]**	**HF and LVEF ≤40% or ≤30%[5]**	**CKD associated with T2D[6,7]**

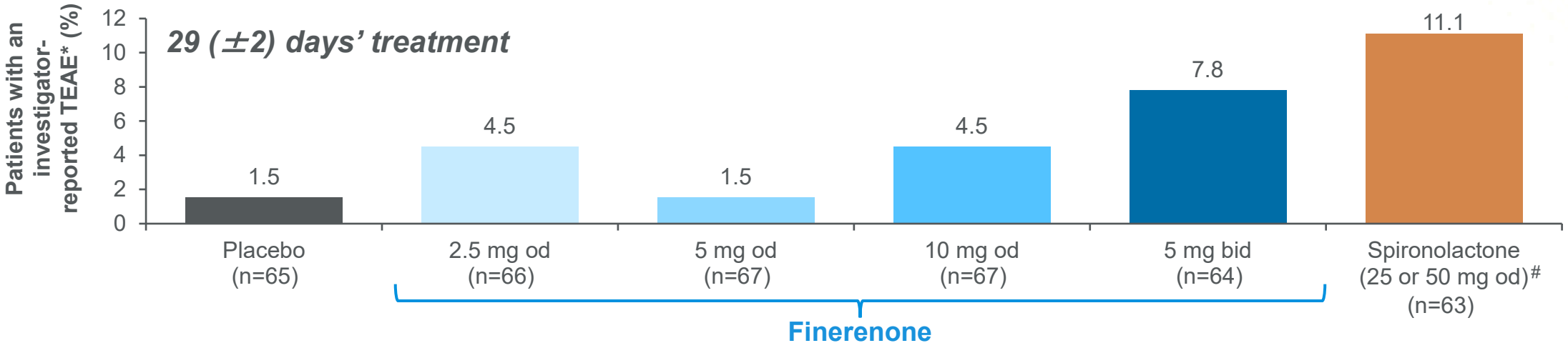
*In patients with HF; #in healthy volunteers

CNS, central nervous system; HF, heart failure; LVEF, left ventricular ejection fraction

1. Kintscher U, *et al. Br J Pharmacol* 2021; doi: 10.1111/bph.15747; 2. Schwabe JW, *et al. Cell* 1993;75:567–578; 3. Tanenbaum DM, *et al. Proc Natl Acad Sci USA* 1998;95:5998–6003;
4. Pfizer Ltd. Aldactone (spironolactone) Summary of Product Characteristics. 2022. https://www.medicines.org.uk/emc/product/2899/smpc [accessed Mar 2023];
5. Zentiva Pharma UK Limited. Inspra (eplerenone) Summary of Product Characteristics. 2021. https://www.medicines.org.uk/emc/product/3665/smpc#INDICATIONS [accessed Mar 2023];
6. Bayer AG. (finerenone) Summary of Product Characteristics. 2023. https://www.ema.europa.eu/documents/product-information/kerendia-epar-product-information_en.pdf [accessed Mar 2023];
7. Bayer AG. (finerenone) Summary of Product Characteristics. 2023.

In the phase II ARTS trial, finerenone was associated with lower rates of hyperkalaemia* than spironolactone[1]

In part B of the ARTS (phase II) trials, patients had CKD (eGFR 30–60 ml/min/1.73 m^2) and HFrEF



The results from ARTS are reinforced by a meta-analysis that found that finerenone had a lower relative risk of hyperkalaemia compared with spironolactone and eplerenone ‡,2

Spironolactone RR=4.58
95% CI 2.60–8.08; *p*<0.00001

Eplerenone RR=2.81
95% CI 1.03–7.69; *p*=0.04

Finerenone RR=2.22
95% CI 0.13–38.13; *p*=0.58

*Using the terms 'hyperkalaemia' or 'blood potassium increased'; #The starting dose of spironolactone was 25 mg od; this was up-titrated to 50 mg od at ~day 15 if serum [K+] was ≤4.8 mmol/l. Spironolactone doses were up-titrated for 30/63 (47.6%) patients, resulting in a mean daily dose of 37 mg by the end of the study; ‡*p*-values reported for spironolactone/eplerenone/finerenone with an ACE-i/ARB compared with ACEi/ARB treatment alone
bid, twice daily; HFrEF, heart failure with reduced ejection fraction; [K+], potassium concentration; od, once daily; RR, risk ratio; TEAE, treatment-emergent adverse event;

1. Pitt B, *et al*. *Eur Heart J* 2013;34:2453–2463; 2. Zuo C, *et al. Int J Clin Pract*. 2019; doi:10.1111/ijcp.13413

Finerenone has demonstrated significant risk reductions in CV and kidney outcomes in two phase III clinical trials

FIDELITY

Prespecified pooled analysis of data from the **FIDELIO-DKD and FIGARO-DKD** trials

>13,000 patients **across the disease continuum of CKD and T2D** (CKD stage 1–4) with moderate-to-severely elevated albuminuria (UACR ≥30 mg/g)

14% reduced **risk of CV morbidity and mortality** (HR=0.86; 95% CI 0.78–0.95; *p*=0.002)[1]

22% reduced **risk of first HHF*** (HR=0.78; 95% CI 0.66–0.92; *p*=0.003)[1]

23% reduced **risk of CKD progression#** (HR=0.77; 95% CI 0.67–0.88; *p*=0.0002)[1]

20% reduced **risk of ESKD** (HR=0.80; 95% CI 0.64–0.99; *p*=0.040)[1,‡]

32% reduction in **UACR** (ratio of LS mean change from baseline 0.68; 95% CI 0.66–0.70)[1]

Finerenone is indicated for the treatment of CKD (with albuminuria) associated with T2D in adults[2]

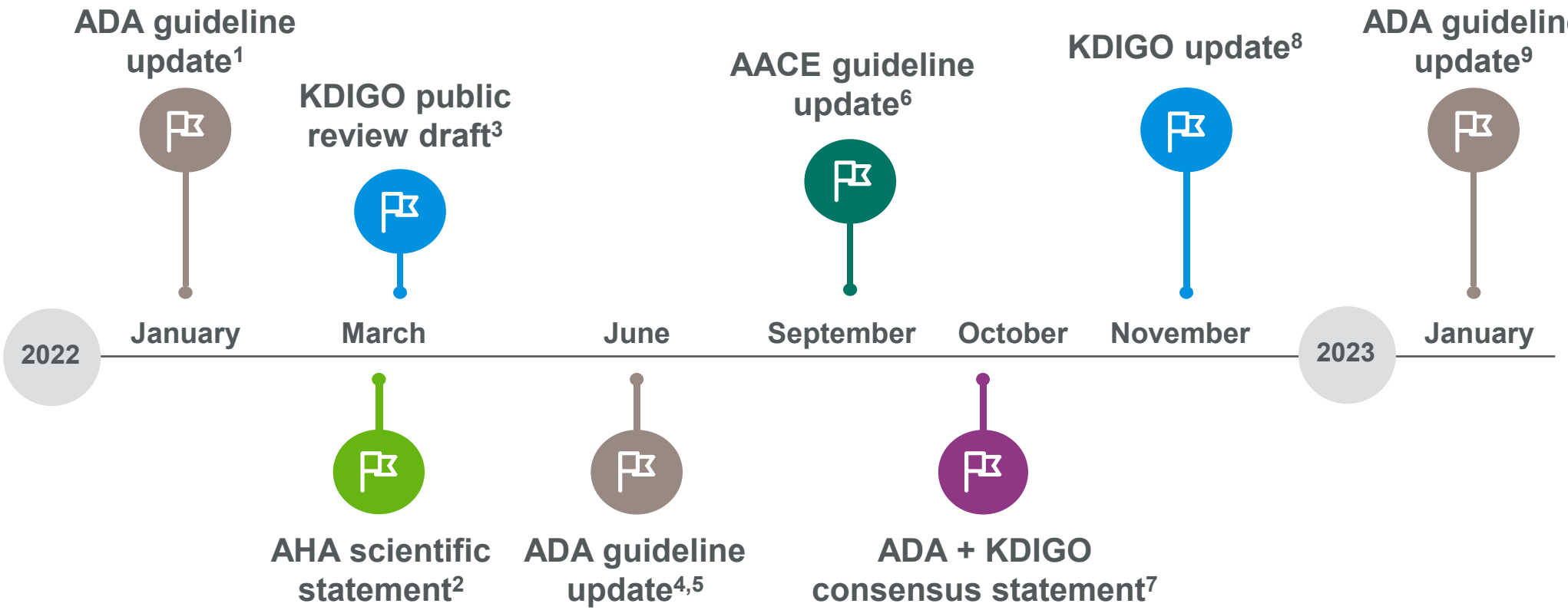
*First HHF defined as first event after randomisation; #ESKD or an eGFR <15 ml/min/1.73 m^2; events were classified as renal death if: (1) the patient died; (2) KRT had not been initiated despite being clinically indicated; and (3) there was no other likely cause of death; ‡analysis for *p*-value not prespecified.

HbA1c, glycated haemoglobin; HHF, hospitalisation for heart failure; KRT, kidney replacement therapy; LS, least-squares

1. Agarwal R, *et al. Eur Heart J* 2022;43:474–484; 2. Bayer AG. KERENDIA® (finerenone) Summary of Product Characteristics. 2023. https://www.ema.europa.eu/documents/product-information/kerendia-epar-product-information_en.pdf [accessed 23 Mar 2023]

Recent clinical guideline updates reflect the evolving treatment landscape for CKD and T2D

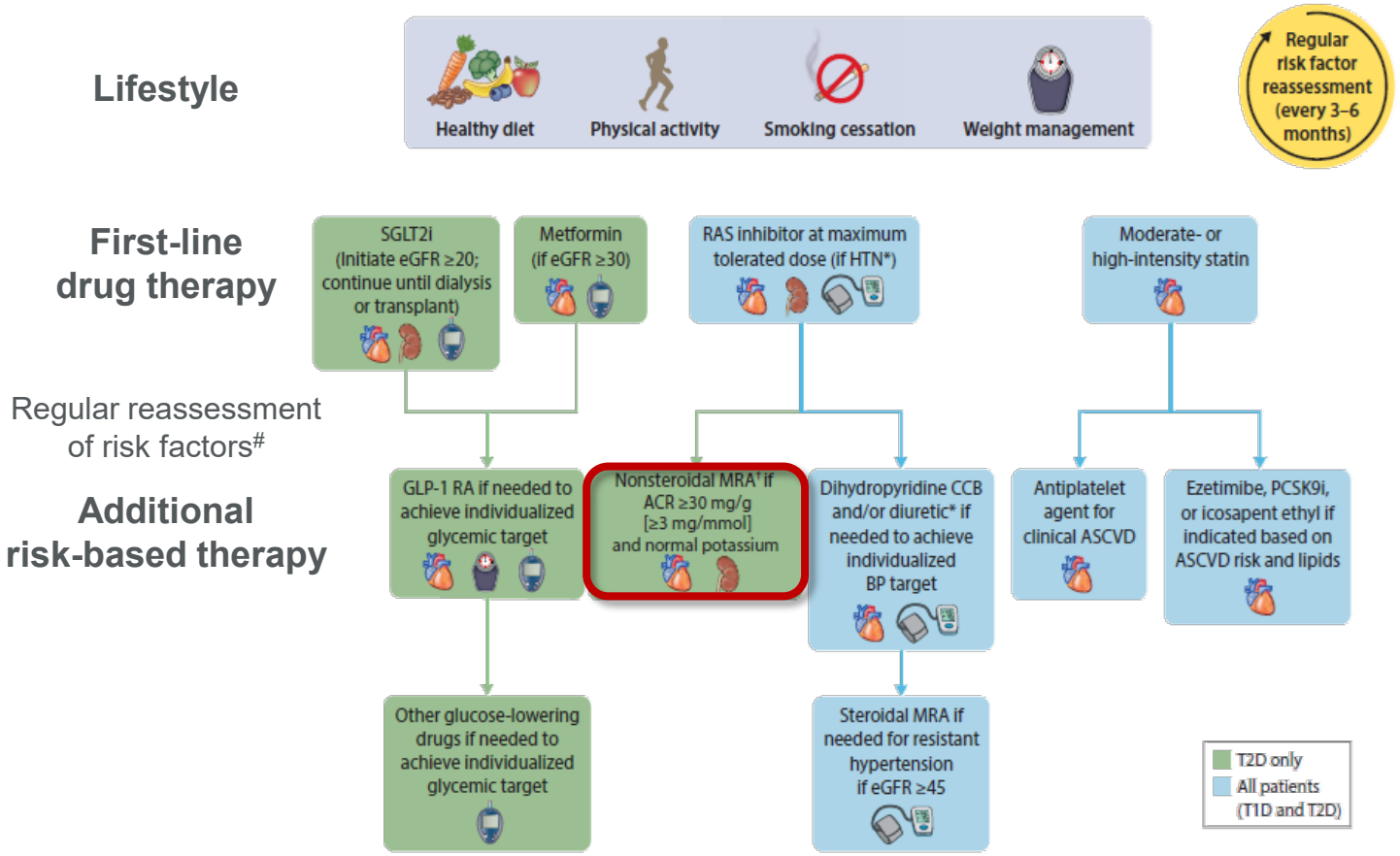
Over the past year, finerenone has been included in the following guidelines and scientific statements:



AACE, American Association of Clinical Endocrinology; ADA, American Diabetes Association; AHA, American Heart Association; KDIGO, Kidney Disease: Improving Global Outcomes

1. American Diabetes Association. Diabetes Care 2022;45(Suppl 1):S1–S258; 2. Joseph JJ, *et al. Circulation* 2022;145:e722–e759; 3. Kidney Disease: Improving Global Outcomes (KDIGO) 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease – Public Review Draft; March 2022; 4. American Diabetes Association. *Diabetes Care* 2022;45(Suppl 1);S144–S174 (addendum); 5. American Diabetes Association. *Diabetes Care* 2022;45(Suppl 1):S175–S184 (addendum); 6. Blonde L, et al. *Endocr Pract* 2022;28:923–1049; 7. de Boer IH, *et al. Diabetes Care* 2022;45:3075–3090; 8. Kidney Disease: Improving Global Outcomes. *Kidney Int* 2022;102:S1–S128; 9. American Diabetes Association. *Diabetes Care* 2023;46(Suppl 1):S191–S202

KDIGO 2022 guidelines recommend a holistic approach to improve outcomes in patients with CKD and T2D



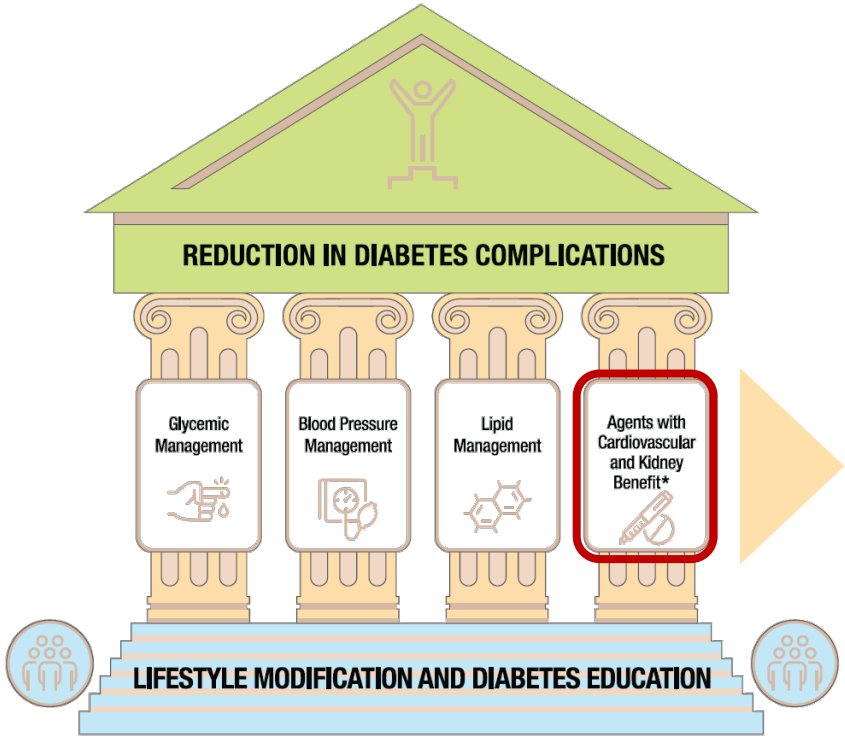
The KDIGO 2022 guidelines position finerenone in **ALL** patients with diabetes and CKD (UACR ≥30 mg/g)§

*ACEi or ARB (at maximal tolerated doses) should be first-line therapy for hypertension when albuminuria is present. Otherwise, dihydropyridine calcium channel blocker or diuretic can also be considered; all three classes are often needed to attain BP targets; #glycaemia, albuminuria, BP, CVD risk and lipids; †finerenone is currently the only nonsteroidal MRA with proven clinical kidney and CV benefits; § after treatment with RASis in patients with UACR ≥30 mg/g and normal serum potassium.

ACR, albumin-to-creatinine ratio; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CCB, calcium channel blocker; CVD, cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HTN, hypertension; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; RAS, renin–angiotensin system; T1D, type 1 diabetes

Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2022;102:S1–S128

ADA 2023 recommendations for finerenone use



Adapted from: American Diabetes Association. *Diabetes Care* 2023;46;S158–S190

CKD and risk management section[1]

Since January 2022, finerenone has been an ADA-recommended option for patients with CKD and T2D[2]

January 2023 update:

A

Recommendation 11.5d:
'In people with CKD and albuminuria who are at increased risk for CV events or CKD progression, a nonsteroidal MRA shown to be effective in clinical trials is recommended to reduce CKD progression and CV events'[1]

CV disease and risk management section[3]

In June 2022, a recommendation was added which included evidence from trials of medication effects on heart failure and CV and CKD outcomes in patients with T2D[4]

January 2023 update:

A

Recommendation 10.43:
'For people with T2D and CKD with albuminuria treated with maximum tolerated doses of ACE inhibitors or ARB, addition of finerenone is recommended to improve CV outcomes and reduce the risk of CKD progression'[3]

Recommendations based on evidence from the **FIDELIO-DKD** trial, **FIGARO-DKD** trial and the **FIDELITY** pooled analysis[1,4]

*Risk reduction interventions to be applied as individually appropriate

1. American Diabetes Association. *Diabetes Care* 2023;46(Suppl 1):S191–S202; 2. American Diabetes Association. *Diabetes Care* 2022;45;S175–S184;
3. American Diabetes Association Professional Practice Committee. *Diabetes Care* 2023;46(Suppl 1):S158–S190;
4. American Diabetes Association Professional Practice Committee. *Diabetes Care* 2022;45(Suppl 1):S144–S174

American Diabetes Association.

A consensus report from the ADA and KDIGO on the management of CKD in T2D was published in October 2022

Key focus of report

Screening and diagnosis (screening for CKD with eGFR and UACR)

A holistic approach including **treatment targets** and **pharmacotherapy**

Comprehensive patient care

Finerenone consensus statement

*A **nonsteroidal MRA** with proven **kidney and CV benefit** is recommended for patients with T2D, eGFR ≥25 ml/min/1.73 m^2, normal serum [K^+], and albuminuria (ACR ≥30 mg/g) despite maximum tolerated dose of RASi*

Statements were based on the **FIDELIO-DKD** and **FIGARO-DKD** studies and the **FIDELITY** pooled analysis

de Boer IH, *et al. Diabetes Care* 2022;45:3075–3090

Summary

Finerenone is a selective nonsteroidal MRA that has been shown to provide **CV and kidney benefits** in **patients with CKD and T2D**[1,2]

Major clinical guidelines recommend finerenone as a therapeutic option **to reduce CKD progression and CV events** in people with CKD and T2D[3,4]

Guideline-recommended **use of finerenone** in patients with CKD and T2D is **independent of SGLT-2i use**

Through the **ADA/KDIGO 2022 Consensus Statement**,[5] there is now a general inter-specialty agreement on a comprehensive approach for the management of CKD in T2D

1. Bakris GL, *et al*. *N Engl J Med* 2020;383:2219–2229; 2. Pitt B, *et al*. *N Engl J Med* 2021;385:2252–2263; 3. Kidney Disease: Improving Global Outcomes. *Kidney Int* 2022;102:S1–S128;
4. American Diabetes Association. *Diabetes Care* 2023;46(Suppl 1):S191–S202; 5. de Boer IH, *et al. Diabetes Care* 2022;45:3075–3090