

Management of Hypertension in Patients With Diabetic Kidney Disease: Summary of the Joint Association of British Clinical Diabetologists and UK Kidney Association (ABCD-UKKA) Guideline 2021



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Diabetic kidney disease (DKD) accounts for >40% cases of chronic kidney disease (CKD) globally. Hypertension is a major risk factor for progression of DKD and the high incidence of cardiovascular disease and mortality in these people. Meticulous management of hypertension is therefore crucial to slow down the progression of DKD and reduce cardiovascular risk. Randomized controlled trial evidence differs in type 1 and type 2 diabetes and in different stages of DKD in terms of target blood pressure (BP). Renin-angiotensin blocking agents reduce progression of DKD and cardiovascular events in both type 1 and type 2 diabetes, albeit differently according to the stage of CKD. There is emerging evidence for the benefit of sodium glucose cotransporter 2, nonsteroidal selective mineralocorticoid antagonists, and endothelin-A receptor antagonists in slowing progression and reducing cardiovascular events in DKD. This UK guideline, developed jointly by diabetologists and nephrologists, has reviewed all available current evidence regarding the management of hypertension in DKD to produce a set of comprehensive individualized recommendations for BP control and the use of antihypertensive agents according to age, type of diabetes, and stage of CKD (<https://ukkidney.org/sites/renal.org/files/Management-of-hypertension-and-RAAS-blockade-in-adults-with-DKD.pdf>). A succinct summary of the guideline, including an infographic, is presented here.

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KEYWORDS: ACE inhibitors; angiotensin receptor blockers; chronic kidney disease; diabetes; dialysis; hypertension
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People with diabetes and CKD are at risk of premature morbidity and mortality compared with those without these conditions; predominantly related to cardiovascular events, such as acute coronary syndrome, heart failure, and strokes, for which,

hypertension is a common modifiable risk factor.¹ End-stage kidney disease is another complication, mediated in part by hypertension, and is associated with poor quality of life, multiple hospital admissions, and increased burden to already stretched health care systems across the world.^{2,3}

With the increasing worldwide prevalence of type 2 diabetes, DKD has emerged as a significant contributor to the burden of global disease.⁴ This has attracted research with novel agents such as sodium glucose co-transporter 2 inhibitors and nonsteroidal mineralocorticoid receptor antagonists in recent years. These

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new agents have been found to improve cardiorenal outcomes with a modest BP-lowering effect.^{5,6}

The targets of therapy and agents used for BP control in people with DKD have evolved in the last 40 years. Agents that inhibit the renin-angiotensin-aldosterone system (RAAS) have been found to decrease adverse cardiorenal outcomes over and beyond BP-lowering effect.⁷ Nevertheless, intensive BP control (systolic BP <120 mm Hg) has not been found to be associated with better outcomes than standard control (systolic BP <140 mm Hg) in people with diabetes.⁸ People with DKD are often old, frail, and multimorbid. As such, lower BP targets are likely to be associated with increased adverse events, including symptomatic postural hypotension, falls, fractures, acute kidney injury, and hyperkalemia.⁹

The 2021 update of the Joint Association of British Clinical Diabetologists and UK Kidney Association guideline provides guidance to practicing clinicians on personalized care of hypertension in people with DKD taking into account the type of diabetes (type 1 and type 2), age, stage of CKD, and degree of proteinuria (<https://ukkidney.org/sites/renal.org/files/Management-of-hypertension-and-RAAS-blockade-in-adults-with-DKD.pdf>).¹⁰

The guideline emphasizes the importance of accurate BP measurement and monitoring, nonpharmacologic management, use of appropriate pharmacologic agents, and BP targets based on available evidence (Figure 1^{11,12} and Table 1).

Methodology

The recommendations are based on review of literature initially between October 2013 and December 2016 and further detailed review until April 2021 for the current update. We searched the PubMed/MEDLINE, Cochrane Library, EMBASE, and Google Scholar and used the following key terms: type 1 diabetes, type 2 diabetes, hypertension, albuminuria, microalbuminuria, microvascular complications, nephropathy, CKD, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), and mineralocorticoid antagonists. The recommendation grades ranged from 1 (strong recommendation) to 2 (weak recommendation), and the corresponding evidence quality was as follows: A (high-quality evidence), B (moderate-quality evidence), C (low-quality evidence), and D (very low-quality evidence). In an area that lacks adequate evidence to support a recommendation, further research is suggested (Research Recommendation).

Measurement of BP

Management of hypertension in people with DKD requires accurate measurements of BP, regular

monitoring for side effects of medications, and personalized therapy. We suggest that the British and Irish Hypertension Society's guidance on standardized, automated BP measurement is followed (<https://bihsoc.org/wp-content/uploads/2017/11/BP-Measurement-Poster-Automated-2017.pdf>).¹³ The BP thresholds and targets in this guideline refer to standardized office BP readings unless specified otherwise. We encourage self (home) BP monitoring using a validated device which empowers patients and improves BP control.

Nonpharmacologic Management

The guideline recommends a reduced salt intake, <90 mmol of sodium daily (<2 g of sodium or <5 g of sodium chloride daily), alcohol <2 units daily for men and 1 unit daily for women, regular exercise at least 30 minutes daily for 5 days a week, and to maintain a body mass index between 20 and 25 kg/m². These recommendations are based on observational studies in people with type 2 diabetes and require regular reinforcement at each patient encounter.

Recommendations for Management of Hypertension in People With Type 1 Diabetes and CKD G1 to 5 (Nondialysis)

1. In people with type 1 diabetes and urine albumin-to-creatinine ratio (ACR) of ≤ 3 mg/mmol, we recommend a threshold for BP therapy of a persistent upright (sitting or standing) BP that is $\geq 140/90$ mm Hg (1B)*

In children and adolescents with type 1 diabetes, the threshold for high BP is an average systolic BP and/or diastolic BP greater than the 95th percentile for the person's sex, age, and height on >3 occasions (1B).**

2. We recommend that ACEI therapy should be used as a first-line agent for BP lowering and, if ACEI therapy is contraindicated or not tolerated ARBs should be considered (1B).
3. In most adults with type 1 diabetes mellitus and persistent ACR >3 mg/mmol, we recommend that ACEI therapy should be considered irrespective of BP and that the target upright BP should be $\leq 130/80$ mm Hg in younger adults (1B), but $\leq 140/90$ mm Hg for those aged >65 years (2D). We recommend that the dose of ACEI should be titrated to the maximum tolerated (1B).
4. There is no current evidence to support a role for ACEI therapy for BP control or renal protection in

*We suggest a target upright BP in younger adults of 120/80 mm Hg and 140/90 mm Hg for those aged >65 years (2D).

**Between the ages of 30 and 65 years, for some people with higher lifetime risk through earlier age of onset of type 1 diabetes, it may be appropriate to target a diastolic BP of <80 mm Hg (2C).

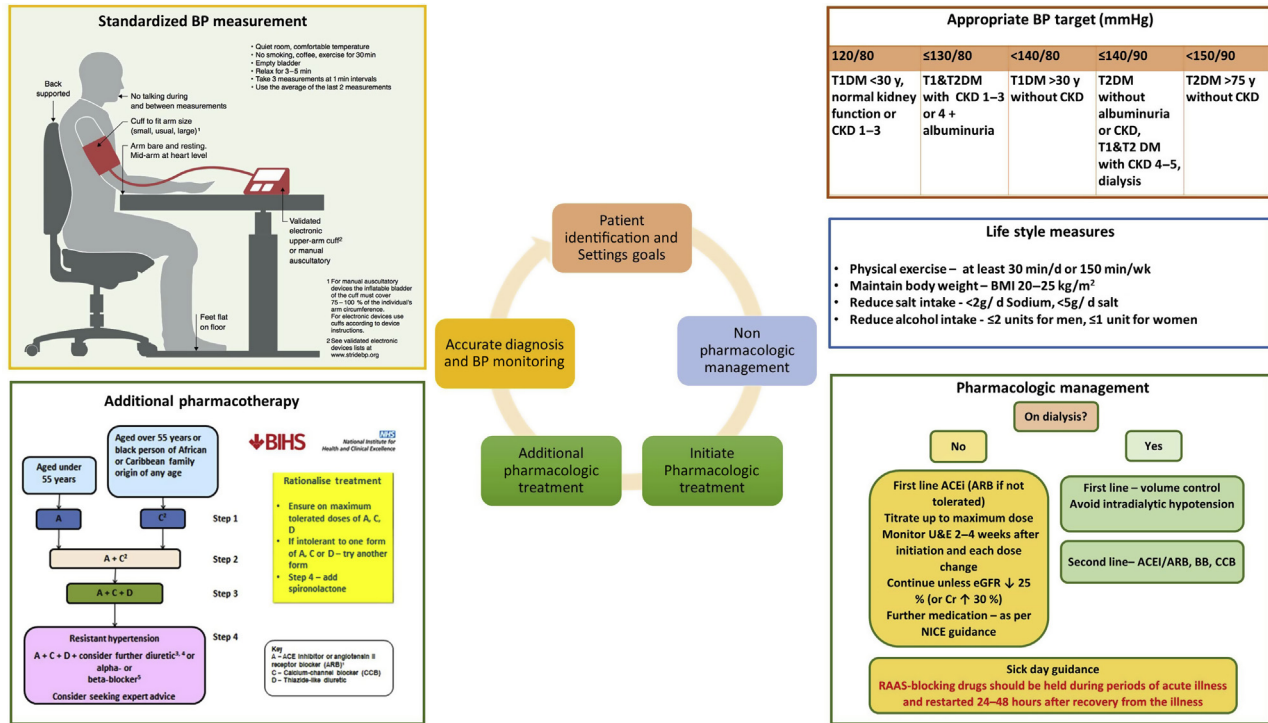


Figure 1. A visual summary of the ABCD-UKKA guideline on the management of hypertension in DKD. The figure on standardized BP measurement is adapted from Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. *Hypertension*, volume 75, issue 6, pages 1334–1357. <https://www.ahajournals.org/doi/10.1161/HYPERTENSIONAHA.120.15026>.¹¹ © 2020 American Heart Association, Inc. The algorithm for selection of antihypertensive treatment is adapted from NICE Hypertension Guideline 2019 based on the BIHS algorithm (<https://www.nice.org.uk/guidance/ng136>). *CG136 Hypertension in Adults: Diagnosis and Management*. © NICE (2019).¹² Available from <https://www.nice.org.uk/guidance/ng136>. All rights reserved. Subject to Notice of rights. NICE guidance is prepared for the National Health Service in England. All NICE guidance is subject to regular review and may be updated or withdrawn. NICE accepts no responsibility for the use of its content in this publication. ABCD-UKKA, Joint Association of British Clinical Diabetologists and UK Kidney Association; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; BIHS, British and Irish Hypertension Society; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; Cr, creatinine; DKD, diabetic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; NICE, National Institute for Health and Care Excellence; T1, type 1; T2, type 2; U&E, urea and electrolytes.

- people with type 1 diabetes mellitus who are normotensive and have urine ACR ≤3 mg/mmol (1C).
- There is some evidence to support the use of candesartan to prevent the development or progression of retinopathy in people with type 1 diabetes who are normotensive and have urine ACR ≤3 mg/mmol (1C).
 - There is no firm evidence to support a role of dual blockade of the RAAS in people with type 1 diabetes mellitus (1C).
 - We recommend that people with type 1 diabetes mellitus should be advised to hold RAAS-blocking drugs during periods of acute illness (1C).
 - We recommend that women of childbearing age should be encouraged to hold RAAS-blocking drugs before actively considering pregnancy (1B).

The guideline recommends tight control of BP in those with significant proteinuria. Proteinuria in type 1 diabetes is strongly associated with progression to stage G3 CKD (32% in 10 years) and end-stage kidney disease (16% in 10 years); treatment of hypertension slows progression and alongside glycemic control can

induce regression of proteinuria with a decreased risk of declining glomerular filtration rate.¹⁴ The recommended BP target in people with type 1 diabetes with ACR >3 mg/mmol is <130/80 mm Hg, whereas the target is <140/90 mm Hg when ACR is ≤3 mg/mmol. Threshold for treatment and targets in children are lower, as illustrated in Figure 1. The results of Pittsburgh EDC study 25-year follow-up study support a target BP of 120/80 mm Hg in childhood-onset type 1 diabetes.¹⁵ Nevertheless, for older adults, the targets are higher at 130 to 139 mm Hg systolic.¹⁶ On the basis of the evidence from short-term randomized controlled trials, the guideline recommends ACEi as the initial treatment of hypertension and for proteinuria without hypertension and ARBs if ACEi are not tolerated.¹⁷ ACEi should not be used in normotensive individuals without proteinuria nor during pregnancy and needs to be temporarily withheld during an acute illness. There is no evidence to support the use of ACEi and ARB together. Control of BP long-term is more critical than the use of a specific RAAS-blocking agent.

Table 1. Blood pressure targets in people with diabetes through stages of kidney function impairment

Type of diabetes	Stage of kidney function impairment				
	Normal kidney function, normoalbuminuria	Normal kidney function, microalbuminuria	CKD stages 1–3	CKD stages 4–5 (nondialysis)	CKD stage 5 (dialysis)
Type 1	<140/80–90 (2D) <120/80 (2D) ^a (for <30 yr)	≤130/80 (1B) 120/80 (2D) ^a	≤130/80 (1B) 120/80 (2D) ^a	≤140/90 (1B) ≤130/80 for those with albuminuria (2C)	≤140/90 (2D) ^b (interdialytic BP)
Type 2	<140/90 (1D) <150/90 (2B) ^c (for ≥75 yr)	<130/80 (2D)	<130/80 (2D)	<140/90 (1B) ^d <130/80 for those with albuminuria (2C)	<140/90 (2D) ^b (interdialytic BP)

BP, blood pressure; CKD, chronic kidney disease.

^aLower targets for younger adults aged <30 yr.

^bMonitor and target interdialytic home BP for people on dialysis.

^cFor frail adults >75 yr, a higher target >150/90 mm Hg may be appropriate to avoid side effects.

^dFor adults >65 yr, a higher target >140/90 mm Hg may be appropriate.

All BP are in mm Hg; the evidence grade is in brackets.

Recommendations for Management of Hypertension and RAAS Inhibitor in People With Type 2 Diabetes and CKD G1 to 3

1. In people with type 2 diabetes mellitus and hypertension, we recommend salt intake of <90 mmol per day (<2 g per day of sodium—equivalent to 5 g of sodium chloride) (1C).
2. In people with type 2 diabetes mellitus, CKD, and urine ACR ≤3 mg/mmol, we recommend that their target upright BP should be <140/90 mm Hg, using antihypertensive therapy in the maximum tolerated doses (1D).
3. In people with type 2 diabetes mellitus, CKD, and urine ACR >3 mg/mmol, we suggest aiming for a target upright BP that is consistently <130/80 mm Hg, using antihypertensive therapy in the maximum tolerated doses (2D).
4. There is no evidence to support either ACEI or ARB therapy as first-line BP-lowering agents in comparison with other antihypertensive agents in people with type 2 diabetes, normal renal function, and normal urine ACR (≤3 mg/mmol) (1A).
5. We suggest that ACEIs (or ARBs if ACEIs are not tolerated) should be preferentially used in people with type 2 diabetes mellitus and CKD who have urine ACR >3 mg/mmol. We recommend that the dose of ACEI (or ARB) should be titrated to the maximum tolerated (2D).
6. There is currently no evidence to support the role of home or ambulatory BP monitoring in people with type 2 diabetes mellitus and CKD stages G2 and G3 (1D).
7. There is currently no evidence to support the role of dual blockade of the RAAS in people with type 2 diabetes mellitus and CKD stages G1 to G3 (1B).
8. Upright BP targets should be set at no <150/90 mm Hg in those with type 2 diabetes mellitus who are aged ≥75 years (2B).
9. We recommend that people with type 2 diabetes mellitus should be advised to hold RAAS-blocking drugs during periods of acute illness and restarted 24 to 48 hours after recovery from the illness (1C).

Recommendations for Management of Hypertension and RAAS Inhibitor in People With Type 2 Diabetes and CKD G4 and 5 (Nondialysis)

1. We recommend initiation of antihypertensive agents in people with diabetes, CKD stages G4 and G5, and ACR ≤3 mg/mmol when BP is >140/90 mm Hg and aim for a BP of <140/90 mm Hg during therapy (1B).
2. We suggest initiation of antihypertensive agents in people with diabetes, CKD stages G4 and G5, and ACR >3 mg/mmol when BP is >130/80 mm Hg and aim for a target BP <130/80 mm Hg (2C).
3. We recommend the use of ACEI (ARB if ACEI is not tolerated) as the first-choice BP-lowering agent in people with diabetes, CKD stages 4 and 5, and micro/macroalbuminuria (1B).
4. We do not recommend the use of combinations of ACEIs and ARBs in people with diabetes and CKD stages G4 and G5 (2B).
5. We suggest dietary advice, correction of acidosis, and loop diuretic therapy to lower serum potassium as necessary in people with diabetes and CKD stages G4 and G5 for safe use of ACEI (or ARB) (not graded).
6. Consider the use of novel potassium binders in people with diabetes and CKD stages G3b to G5 (nondialysis) if potassium level is 6 mmol/l or higher, for continued and safe use of ACEI (or ARB), or where people are not taking or are only taking submaximal RAAS blockade because of hyperkalemia (not graded).

The recommendations for CKD stages G1 to G3 and G4 and G5 (nondialysis) are similar, with subtle differences as suggested previously. For those with ACR ≤3 mg/mmol, we recommend a target BP of <140/90 mm Hg and <130/80 mm Hg if the ACR is >3 mg/mmol. There is no good evidence for tighter BP control, though such evidence exists in people without diabetes.^{8,18} The guideline suggests the use of ACEI or ARB as the first-choice antihypertensive agent in the presence of significant proteinuria, that is, ACR >3 mg/mmol titrating to maximum dose tolerated,¹⁹ but not in

the absence of significant proteinuria.²⁰ Nevertheless, the guideline recommends against the use of dual ACEI and ARB therapy owing to evidence suggesting absence of benefit and the risk of potential harm mainly owing to hyperkalemia.²¹ For older people (>75 years) with DKD, who are often frail and suffer more side effects of antihypertensive treatment, the target is <150 mm Hg systolic, which is supported by evidence from STOP hypertension trial.^{20,22} Hyperkalemia is common in patients with CKD with diabetes, particularly when in RAAS blockade.²³ The novel potassium binders may be used in patients with DKD with hyperkalemia related to RAAS blockade. In people with diabetes and CKD stages 3 to 4, on RAAS blockade (ACEI/ARB ± spironolactone), use of a novel potassium binding polymer, patiromer, resulted in significant decrease in serum potassium maintained in 52 weeks.²⁴

Recommendations for Management of Hypertension and RAAS Inhibitor in Individuals With Diabetes Dependent on Dialysis

1. We recommend that home or ambulatory BP measurement should be used to monitor BP in people with diabetes who are on dialysis (1C).
2. Where ambulatory or home BP measurement is not feasible to monitor BP in people with diabetes who are on dialysis, we suggest using pre-, intra-, and postdialysis standardized BP measurements for people who are on hemodialysis and using standardized clinic BP measurements for people who are on peritoneal dialysis (2D).
3. We recommend volume control as first-line management to optimize BP control in people with diabetes who are on dialysis (1B).
4. We suggest salt restriction to <5 g per day to optimize BP control in people with diabetes who are on dialysis (2C).
5. We suggest a target upright interdialytic BP of <140/90 mm Hg for people with diabetes who are on dialysis. Individualization of the BP target may be indicated in other people who are burdened with multiple comorbidities to reduce adverse events of BP lowering (2D).
6. We recommend that intradialytic hypotension should be avoided in people with diabetes who are on hemodialysis (1B).
7. We suggest using ACEIs or ARBs (but not in combination), beta blockers, and calcium channel blockers to reduce cardiovascular complications in people with diabetes and hypertension who are on dialysis (2B).
8. We suggest the use of diuretics for fluid removal and BP control in people with diabetes who are on dialysis and have residual kidney function (2C).

Randomized controlled trial evidence to guide BP management in patients on dialysis, particularly in those with diabetes, is scanty. Therefore, many of the recommendations in this section are weak and based on low- to very low-quality evidence. Accurate BP monitoring is difficult in people with diabetes on dialysis owing to the changing volume status and the presence of autonomic neuropathy in many. The best possible recordings which correlate with 24-hour BP monitoring are interdialytic home BP recordings.²⁵ Hence, the guideline recommends the use of home BP for monitoring with a interdialytic BP target of <140/90 mm Hg. Meticulous fluid volume management is suggested as the first step in the management of hypertension in patients on dialysis. A randomized controlled trial of 150 patients on hemodialysis randomized to additional ultrafiltration group (40 of 100 had diabetes) or control group (19 of 50 had diabetes) revealed improved BP with volume control.²⁶ The guideline advises avoidance of intradialytic hypotension as it is associated with increased mortality in patients on hemodialysis.²⁷ There is insufficient evidence from randomized controlled trials to make firm recommendations on choice of antihypertensive medication. Beta blockers, RAAS-blocking agents, and dihydropyridine calcium channel blockers are all reasonable choices. Diuretics may be used in the patients to help fluid removal in those individuals with residual renal function²⁸ (Table 1).

Main Research Recommendations

The following areas lack good-quality evidence for the management of hypertension in people with DKD and hence further research is necessary.

1. Is there a role for home or ambulatory BP monitoring in the diagnosis and management of hypertension in people with type 1 diabetes, particularly in those who have diabetic autonomic neuropathy?
2. Does tight glycemic control and BP lowering reduce the incidence of people developing microvascular complications in type 1 diabetes?
3. What is the impact on renal function of lower BP targets in younger people with type 1 diabetes and nephropathy?
4. What is the role of aldosterone receptor blockers in people with type 1 diabetes and nephropathy?
5. What is the evidence-based lower limit for BP reduction (<130/80 mm Hg) in people with type 2

diabetes who have CKD in terms of cardiovascular and renal endpoints?

6. What are the best second- and third-line BP lowering agents in people with type 2 diabetes who have CKD and proteinuria?
7. Does bedtime hypertension treatment improve cardiovascular and renal outcomes in patients with type 2 diabetes and CKD?
8. Which BP measurement should be used to predict left ventricular hypertrophy and mortality in people with diabetes who are on dialysis: pre-dialysis, postdialysis, home or ambulatory BP measurement?
9. What is the optimal upright BP target for people with diabetes who are on dialysis?
10. Does treatment with ACEIs, ARBs, beta blockers, or calcium channel blockers to lower BP in people with diabetes who are on dialysis reduce cardiovascular morbidity and mortality?
11. Does salt restriction (<5 g per day) in people with diabetes who are on dialysis influence BP control or cardiovascular outcome?

Conclusion

The recommendations within the Joint Association of British Clinical Diabetologists and UK Kidney Association guideline provide guidance that supports individualized therapy with BP targets that differ according to age, type of diabetes, and stage of CKD. The Joint Association of British Clinical Diabetologists and UK Kidney Association guideline is based on the best available evidence although less evidence is available for advanced stages of CKD owing to dearth of randomized controlled trials. The guideline promotes the delivery of patient-centered care in setting goals, which provides the patients with best possible outcomes while maintaining good quality of life.

DISCLOSURE

DB reports receiving speaker fees from Vifor Pharma; honoraria for advisory board from Bayer; and research grant from AstraZeneca. PW reports receiving honoraria for delivering educational meetings and/or attending advisory boards for Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Napp, Sanofi, Novo, and Vifor Pharmaceuticals. PD reports receiving honoraria for advisory work and/or lecture fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Napp Pharmaceuticals, Novo Nordisk, and Sanofi. DF reports receiving honoraria for delivering educational meetings and/or attending advisory boards for AstraZeneca, Napp, Boehringer Ingelheim, and Vifor Pharmaceuticals. JK

reports receiving research grants from AstraZeneca and Sanofi and receiving speaker fees and attending advisory boards from Boehringer Ingelheim, AstraZeneca, Sanofi, and Napp. PBM reports receiving speaker fees and attending advisory board from Vifor, AstraZeneca, Pharmacomsos, Napp, Novartis, and Astellas and receiving grants from Boehringer Ingelheim. SCB reports receiving personal fees from Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, and Sanofi-Aventis and being a shareholder in Glycosmedia. ID reports receiving research grants from Medtronic and Sanofi-Genzyme, receiving honoraria for attending advisory board and speaker meetings from GlaxoSmithKline, AstraZeneca, and Sanofi-Genzyme, and being the national lead for 3 GSK trials. All the other authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

ABCD Renal Association Clinical practice guidelines for management of hypertension and renin-angiotensin-aldosterone system blockade in adults with diabetic kidney disease—update 2021 (<https://ukkidney.org/sites/renal.org/files/Management-of-hypertension-and-RAAS-blockade-in-adults-with-DKD.pdf>).

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