Ocedurenone: A Novel Therapy for Uncontrolled Hypertension in Advanced Chronic Kidney Disease

Interviewees:	George Bakris,[1] Faiez Zannad[2,3] 1. American Heart Association Comprehensive Hypertension Center, Department of Medicine, The University of Chicago Medicine, Illinois, USA 2. Clinical Investigation Centre (CIC 1493 Inserm-CHU), Université de Lorraine, Nancy, France 3. Regional and University Hospital Center (CHRU) Nancy, France

Disclosure:	Bakris is a consultant and steering committee member to Bayer, Janssen, KBP Biosciences, Ionis, Alnylam, AstraZeneca, GlaxoSmithKline, Novo Nordisk, Janssen, and inRegen; and editor of the *American Journal of Nephrology*. Zannad has received personal fees from Applied Therapeutics, Bayer, Boehringer, BMS, CVRx, Cardior, Cereno Pharmaceutical, CellProthera, CEVA, Merck, Novartis, NovoNordisk, Owkin, Pfizer, and Servier; holds stock options at G3 Pharmaceutical; and equities at Cereno Pharmaceutical, Cardiorenal, and Eshmoun - Clinical Research; and is the founder of Cardiovascular Clinical Trialists.
Acknowledgements:	Medical writing assistance was provided by Juliet George, Chester, UK.
Disclaimer:	The opinions expressed in this article belong solely to the two named interviewees.
Support:	The publication of this interview feature was supported by KBP Biosciences.
Citation:	EMJ. 2023;8[1]:25-32. DOI/10.33590/emj/10301927. https://doi.org/10.33590/emj/10301927.

Summary

Patients with advanced-stage chronic kidney disease (CKD) have a high burden of disease, which is compounded by serious comorbidities, including diabetes, cardiovascular disease (CVD), and, most commonly, hypertension. Control of hypertension is vital in patients with advanced CKD to reduce the associated risks of morbidity and mortality, but treatment options are limited, largely due to safety concerns for the use of existing antihypertensive agents in patients with poor renal function. During interviews conducted by EMJ in November 2022, two leading specialists in nephrology and cardiology, George Bakris, American Heart Association Comprehensive Hypertension Center, Department of Medicine, The University of Chicago Medicine, Illinois, USA, and Faiez Zannad, Clinical Investigation Centre (CIC 1493 Inserm-CHU), Université de Lorraine, Nancy, France; and Regional and University Hospital Center (CHRU) Nancy, France, discussed the challenges of treating uncontrolled hypertension in advanced CKD. These two experts described the complicated relationship between cardiovascular and renal disease, and identified significant unmet needs for patients with uncontrolled hypertension and advanced CKD. In this context, new agents in the field were viewed with interest, including the emerging class of non-steroidal mineralocorticoid receptor antagonists (MRA). The experts highlighted data from recent studies on the novel non-steroidal

MRA, ocedurenone (KBP-5074), and discussed its potential as a treatment for uncontrolled hypertension in patients with advanced CKD.

EPIDEMIOLOGY AND UNMET NEEDS IN ADVANCED CHRONIC KIDNEY DISEASE

Setting the scene, Bakris defined CKD as a reduction in kidney function (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2), alongside the presence of albuminuria (≥30 mg/day) as an indication of kidney damage. The lower the eGFR, the more significant the disease, but Bakris emphasised: "Advanced CKD (Stages 3b, 4, and 5; or eGFR <45 mL/min/1.73 m^2) is really not just CKD, as the higher the stage, the higher the cardiovascular risk.[1] In the USA, there are close to 17 million people with Stage 3 CKD, but at Stage 4 there are just over 1 million. Why this discrepancy? It's easily put in a simple word: death. A huge number of people die from CVD before they get to Stage 4."

Zannad elaborated on the complex connection between CKD and cardiovascular conditions,[2] describing them as "two sides of the same coin of a common chronic heart–kidney disorder." They explained: "Most cases of CKD are related to risk factors shared with CVD. Hypertension and diabetes are the most frequent attributable risk factors for CKD, and they are also the most frequent attributable risk factors for CVD. If you realise that CKD is as much a consequence of these very common risk factors as CVD, then you realise how serious the intersection of CVD and CKD is. Hypertension is extremely frequent, especially in those above 65 years of age, amongst whom almost one in two inhabitants in the world have some sort of hypertension. Diabetes is on the rise exponentially, and more so in poorer countries in Africa, in the Middle East, and India.[3-5] Therefore, the combined effect of the rising epidemic of diabetes and a high prevalence of hypertension, make the CKD–CVD intersection one of the commonest conditions." Bakris agreed and also highlighted IgA nephropathy as the third most frequent cause of kidney failure, with a high prevalence in Asia.[6] Increasing age and ethnicity were also said to be influential risk factors, with CKD having higher rates in the African-American, African, and Middle Eastern populations.

Hypertension in Advanced Chronic Kidney Disease: An Unmet Need

The experts observed that milder forms of CKD may go undiagnosed for years, while treatment is focused on the more apparent problems of hypertension, diabetes, and other comorbidities. Indeed, diagnosis of CKD may only come following significant disease progression; thus the unmet needs of advanced CKD were described by Zannad as "issues of an 'end of the road' progression of risk factors." Better control of hypertension, and thus reduction in cardiovascular risk, was identified as a key unmet need in patients with advanced CKD. However, according to Bakris: "The higher the stage of CKD, the more difficult it is to control the blood pressure, and the more medications you're going to need. It's rare to find somebody with Stage 4 CKD (eGFR <30 mL/min/1.73 m^2) on one medicine. They're usually on three or four." Bakris went on to note that a patient with Stage 4 CKD linked to diabetes would likely be taking 12–14 different drugs per day for CKD- and CVD-related, and non-related conditions, and that overall, adherence with polypharmacy is a challenge in advanced CKD. Therefore, a simpler and more efficient means of controlling blood pressure is urgently required.

In addition to contributing to disease progression, uncontrolled hypertension was described as a "major contributor to morbidity", causing problems with sleep, the heart, and headaches. "Uncontrolled hypertension has direct effects on the heart," explained Bakris. "It makes the heart bigger, which contributes to the arrhythmia of atrial fibrillation, the most common arrhythmia in the world. It causes a lot of subtle changes as adaptation to these high pressures, which lead to future problems, even after blood pressure is controlled. That's a major issue." In addition, Bakris outlined the wider, indirect effect of uncontrolled hypertension on healthcare provision: "Apart from the impact on the patient and causing disease burden, there's a huge medical cost to the community and to governments because these people are more likely to go to the hospital or have serious

illnesses. To be clear, the majority of these costs are incurred not because of intensive care unit or [scheduled] visits to the hospital, they are driven by emergency room visits."

TREATMENT OF UNCONTROLLED HYPERTENSION IN ADVANCED CHRONIC KIDNEY DISEASE

The selection of treatments for uncontrolled hypertension in CKD is influenced by both general clinical guidelines on managing hypertension, and those specific to managing kidney disease. Considering treatment options in general, Zannad stated: "We have a very large number of antihypertensive medications. The most common medications are very effective, but they need to be combined." More specifically, for people with CKD, Bakris cited the 2021 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines:[7] "The recommendation is to have people on three different classes of drugs that work complementarily: a diuretic that's appropriate for kidney function; a calcium channel blocker; and a blocker of the renin-angiotensin system, so either an angiotensin receptor blocker or an angiotensin-converting enzyme inhibitor, and maximally titrated or tolerated."

Zannad clarified that for a diagnosis of uncontrolled hypertension, patients must have a systolic blood pressure ≥140 mmHg, despite having received the recommended combination of at least two antihypertensive medications and a diuretic.[7] He also explained that patients with uncontrolled hypertension are a mix of those with treatment resistance (i.e., those who required three or more drugs with complementary mechanisms of action, and taking all medications), and those who are poorly adherent. Considering patients with uncontrolled hypertension and advanced CKD, Bakris continued: "Once you've tried those three [medications], the question is, what's number four? The only data we have is per the American Heart Association (AHA) Scientific Statement on resistant hypertension.[8] Here, the fourth drug is considered to be spironolactone, an MRA. Why? Because the PATHWAY-2 trial showed that in people with resistant hypertension, spironolactone produced greater reduction in blood pressure than a β-blocker and an α-blocker.[9] However, the problem with that study is everybody had normal kidney function…"

Bakris explained that patients with advanced CKD (eGFR <45 mL/min/1.73 m^2) were excluded from the PATHWAY-2 study[9] due to the risk of hyperkalaemia with the steroid-based spironolactone. "If you try using [spironolactone] in people with advanced CKD, you're going to run into problems with potassium elevation. It works, but you've got to know what you're doing. Moreover, the dose used in the PATHWAY-2 trial was 25 mg/day, generally higher than used in heart failure. The other major limitation with spironolactone is that it is a prodrug. It gets metabolised to other drugs like canrenone that are active and actually cause gynaecomastia in males, breast tenderness in females, and, over time, intolerable side effects that preclude further use of the drug. So then you switch to eplerenone [another steroidal MRA] that does not have these problems, but you have to give it twice a day, and it has a much weaker effect for blood pressure reduction than spironolactone.[10] That's all we've got, so that's what people use. The hope is that with all these new agents coming out we can find a valuable substitute with far better tolerability in people with advanced CKD that can do the same job as spironolactone."

Emerging Treatments

Looking to the future, the two experts highlighted new drugs in development for the treatment of uncontrolled hypertension, but noted that data in patients with advanced CKD are very limited. "It's been 15–20 years since there's really been anything new in hypertension, and now there's an explosion of medications that are being looked at specifically for resistant hypertension," commented Bakris. "There's the aldosterone synthase inhibitor, baxdrostat, which has published very impressive Phase 2 data,[11] but in a normal kidney population. Also, the dual endothelin receptor antagonist, aprocitentan, is a contender. It showed very good blood pressure reduction in the Phase 3 PRECISION trial in patients with resistant hypertension,[12] but had oedema as a side effect, which is expected with endothelin receptor antagonists. There is the non-steroidal MRA, esaxerenone, approved for hypertension treatment in Japan,[13,14] but its efficacy in people with advanced CKD has not

been tested. There is also the non-steroidal MRA, ocedurenone, at an advanced stage of development. Ocedurenone shows clear promise because, regardless of kidney disease, it has been studied in people who are already taking a minimum of two or more drugs, and often three or more. Thus, the only drug that has consistently steadied resistant hypertension in people with advanced-stage CKD is ocedurenone."

Zannad shared this view: "The non-steroidal MRAs ocedurenone and finerenone are the main promising medications. I say promising because we know that finerenone has shown a cardiovascular and kidney protective effect in patients with diabetic kidney disease in the FIGARO-DKD and FIDELIO-DKD trials;[15,16] although the effect on blood pressure in these trials [in which mean systolic blood pressure at baseline was 136/138 mmHg] was relatively small, and we have no evidence in the non-diabetic population in uncontrolled hypertension. So we are hopeful for ocedurenone, because it has shown significant benefit in controlling blood pressure in uncontrolled hypertension, and notably in this group of patients with advanced CKD."[17]

OCEDURENONE: A NEW TREATMENT OPTION

As described above, several MRAs are already utilised as treatments for hypertension, and the number increases with the emergence of non-steroidal MRAs, including ocedurenone (KBP-5074).[18] Zannad discussed the background to the development of MRAs, which was built upon knowledge of the steroid hormone, aldosterone. Aldosterone is released by the adrenal gland and helps control blood pressure through the regulation of sodium and potassium exchange in the kidney, and exerts its action by binding to the mineralocorticoid receptor, affecting target gene expression.[19] The MRAs, also known as aldosterone receptor antagonists, were subsequently shown to block this effect.[20] "The very first use of MRAs was at high doses as diuretics, which eventually resulted in use as antihypertensive medication, as well as in the chronic congestive states associated with heart and hepatic failure," Zannad explained. "It wasn't until the late 1990s that smaller (non/mild diuretic) doses of MRAs were found to be effective in cardiovascular protection.[21] Since then, there has been a huge amount of work showing that there are mineralocorticoid receptors in a large number of tissues/organs, including the heart, brain, kidney, gut…alongside all the machinery for producing aldosterone in various organs. Aldosterone has very potent anti-inflammatory and anti-fibrotic effects to name just a few, and inflammation and fibrosis are the key common elements of progression of kidney failure and heart diseases. The very first MRAs were the steroidal MRAs, led by spironolactone. Later on we had eplerenone, which is still steroidal, but more specific to mineralocorticoid receptors, so avoided the main limitation of the first-generation agents off-target (e.g., sexual) side effects."

The more recently developed group of non-steroidal MRAs represents a novel approach to treatment and, as such, has been recognised by the U.S. Food and Drug Administration (FDA) as a distinct and new class of antihypertensive agents. Amongst these, ocedurenone is a highly selective agent with a higher binding affinity to the mineralocorticoid receptor than steroidal MRAs, and little or no binding affinity for the glucocorticoid, progesterone, and androgen receptors.[18,22] While ocedurenone has sometimes been referred to as a 'third generation' MRA, both experts felt that this term was highly misleading. "These are essentially different drugs," said Zannad. Bakris concurred: "Ocedurenone has very different chemistry from the steroidal agents. The binding characteristics are very different in terms of how it binds to the aldosterone receptor. The half-life is long, at approximately 60 hours, and is unaffected by dialysis.[17] It does not get into the brain. It does not have active metabolites. Also, because the receptor interaction is different, it produces different effects."[18]

Zannad added that non-steroidal MRAs have also demonstrated differences in their tissue distribution compared to steroidal agents. For example, spironolactone and eplerenone are concentrated in the kidney, impacting on the risk of hyperkalaemia, while finerenone has a more balanced distribution between the heart and kidneys,[18,23] and ocedurenone has a higher tissue concentration in the gastrointestinal tract (unpublished data, KBP). Therefore, the

distinctions between these categories of MRA are likely to be clinically meaningful in terms of efficacy and safety, as well as affecting practicalities such as dosing regimens. Bakris concluded: "A lot of people see ocedurenone as just an expensive spironolactone, but if you do that you're totally 'throwing the baby out with the bathwater'."

Clinical Support for Ocedurenone in Advanced Chronic Kidney Disease

The experts then considered the current clinical evidence for the efficacy and safety of ocedurenone in treating uncontrolled hypertension in patients with advanced CKD. In Bakris' opinion: "The strongest evidence is from the Phase 2b BLOCK-CKD study of ocedurenone,[17] which studied people with advanced CKD, many actually being in Stage 4. It is a unique study because it looked at the treatment of hypertension in the context of advanced CKD. There are two other drugs in the [non-steroidal MRA] class that produce blood pressure reduction. One is esaxerenone, approved exclusively in Japan,[13] for which there are no placebo-controlled comparisons,[14,24,25] and the other is finerenone.[26,27] The difference is that while finerenone reduces blood pressure (placebo subtracted) variously from 3 mmHg (ARTS-DN, FIGARO-DKD, and FIDELIO-DKD studies)[15,26,28,29] to approximately 8 mmHg (subset analysis from ARTS-DN study, eGFR of approximately 68, though office blood pressure from the same study showed around 3 mmHg reduction),[27] ocedurenone 0.5 mg reduces it by 11 mmHg (placebo subtracted),[17] and it's that [magnitude of] difference that made spironolactone the winner in the PATHWAY-2 study against β-blockers and α-blockers.[9] Although it doesn't sound like much, it's a big deal."

Bakris continued: "Ocedurenone 0.5 mg is a very low dose, but it has very powerful effects on precisely those people who have resistant hypertension. No other agent, so far, has steadied blood pressure as well in this group of patients. And the point is that these are the patients who need the most help, and these are the only data that I'm aware of that are unique to this patient group. As a dedicated study, BLOCK-CKD is really the only one." Importantly, Bakris also highlighted that the benefit observed with ocedurenone in this study appeared to be equal across all patients, unaffected by the presence of diabetes or older age, which are both common characteristics of patients with advanced CKD.

The opportunity to use ocedurenone at a low dose, due to its high affinity and specificity of receptor binding,[18,22] also has a favourable impact on safety, which limits the risk of hyperkalaemia as well as off-target (e.g., androgen) receptor side effects such as gynaecomastia. The higher concentration of ocedurenone in the gastrointestinal tract (unpublished data, KBP), compared to other MRAs that are more concentrated in the kidney,[18] may also lower the risk of hyperkalaemia. Considering clinical evidence from the BLOCK-CKD study, Bakris explained: "In terms of the safety signal for potassium, there was hyperkalaemia [0.5 mg ocedurenone 16.7% versus placebo 8.8%; no hyperkalaemia ≥6.0 mmol/L][17] but not at the frequency that you would expect of spironolactone. This has been looked at in detail with another non-steroidal MRA, finerenone, and it's been estimated that there's an approximately six-fold higher risk of hyperkalaemia with spironolactone than there is with finerenone [indirect comparison in patients with treatment resistant hypertension and advanced CKD].[30] So again, the distinct characteristics of binding and other factors contribute to this. Exactly how we don't know, but ocedurenone is behaving the same way as the other members of this non-steroidal MRA family."

Zannad reinforced the importance of these hyperkalaemia data for the clinical utility of ocedurenone: "The main limitation of the use of MRAs so far, in heart failure and in CKD, has been hyperkalaemia. Hyperkalaemia scares physicians because of the connection with the risk of sudden death and arrhythmias. Indeed, above approximately 5.5 or 6.0 mmol/L potassium, there is an increased risk of cardiovascular events and death. We now have pharmacological reason to believe that the non-steroidal MRAs may have a lower rate of hyperkalaemia, and this will give a major edge. With ocedurenone, for the first time ever we have an MRA that lowers blood pressure significantly, and may be safely used in advanced CKD."

However, Zannad also emphasised that further evidence was required to build on these Phase 2

findings: "We need to study many more patients [with ocedurenone] to know about the long-term and large population safety, and learn more about whether this promising effect on blood pressure is translated into hard outcome prevention. And that's the next step. We are very hopeful that ocedurenone may be a real addition in this space of uncontrolled hypertension in CKD." Bakris added: "A Phase 3 study of ocedurenone [in patients with uncontrolled hypertension and moderate or severe CKD] called CLARION-CKD[31] is ongoing, and I'm highly optimistic that it will show what the Phase 2 study showed, only with much greater numbers."

Further Patient Benefits

The experts moved on to consider the broader impact of ocedurenone for patients with advanced CKD, including on dosing, compliance, and quality of life. "There are a number of factors that affect compliance, and if you have a drug that has got this much impact on blood pressure, without profound side effects, the patients will notice it and stick with it," commented Bakris. Zannad agreed: "So far, there are no concerns about any safety issues that could make patients less likely to take ocedurenone." The convenience of a once-daily, or even potentially every other day (half-life approximately 60 hours), oral dosing regimen was identified as another factor in favour of ocedurenone, compared to eplerenone, which is taken twice a day, or sometimes once daily but with resulting loss of 24-hour coverage.

Bakris observed that effective control of hypertension would also benefit patients in terms of quality of life by relieving hypertension-associated effects such as headaches and poor sleep. Thus, reflecting on the overall profile of ocedurenone, they concluded: "There are a lot of things to be positive about with ocedurenone. I think if you have something that's got good tolerability and effectively lowers blood pressure in a very high-risk group, then you will have a big impact on morbidity. Yes, patients worry about mortality, but they also worry about morbidity because that's what's causing them all the problems right now. If you look at the profile of the non-steroidal MRAs in general, their morbidity index is far better than the steroidal MRAs. The only people arguing about this will be the ones who can't afford the non-steroidal MRAs, which is a real issue. Fundamentally, the cost question is going to be quite important, and is looming." Zannad agreed that much would depend on the availability and pricing of the medication. However, they concluded: "It's very likely that this class of drug is going to be effective in a large variety of cardiovascular and renal conditions, as has been shown with other MRAs. Indeed, mineralocorticoid receptors are so ubiquitous that we may have many more developments beyond CKD and cardiovascular conditions. I hope that this is just the beginning of a long story for ocedurenone."

SUMMARY

During the interviews, Bakris and Zannad highlighted the complications and significant unmet needs surrounding the treatment of uncontrolled hypertension in patients with advanced CKD. Despite the many antihypertensive drugs and combinations available, the experts acknowledged that their use in advanced CKD is limited by safety concerns, hyperkalaemia in particular, and compounded by an overall lack of clinical evidence. After decades with little advancement, the emergence of non-steroidal MRAs was viewed as an important development for the treatment of uncontrolled and resistant hypertension. Amongst this new class of agents, ocedurenone was identified as a promising drug for use in patients with hypertension and advanced CKD. In the first dedicated study of patients with uncontrolled hypertension and advanced CKD, ocedurenone demonstrated efficacy in lowering blood pressure, together with a favourable safety profile. The experts were optimistic that it could provide a much-needed treatment option for this group of severely ill patients, with potential for reduction in the risk of cardio-renal outcomes.

Biographies

George Bakris

American Heart Association Comprehensive Hypertension Center, The University of Chicago Medicine, Illinois, USA

George Bakris is a Nephrologist/Certified Hypertension Specialist, and is Professor of Medicine and Director of the American Heart Association (AHA) Comprehensive Hypertension Center at the University of Chicago Medicine, Illinois, USA. They have published over 900 peer-reviewed articles and book chapters in the areas of diabetic kidney disease, hypertension, and nephropathy progression. They have served on the Cardiorenal Advisory Board of the U.S. Food and Drug Administration (FDA), as well as many national guideline committees. Bakris is the past President of the American College of Clinical Pharmacology (ACCP) and the American Society of Hypertension (ASH). They serve on more than 15 editorial boards and are current Editor-in-Chief of the American Journal of Nephrology, and UpToDate (Nephrology and Hypertension Sections). Bakris is the recipient of the Irvine Page-Alva Bradley Lifetime Achievement Award-American Heart Association BP Council (2019) and National Kidney Foundation of Illinois Lifetime Service Award (2020).

Faiez Zannad

Clinical Investigation Centre (Inserm-CHU), Nancy, France

Faiez Zannad is Professor Emeritus of Cardiology and Therapeutics, and Past Director of the Inserm Clinical Investigation Center at the Université of Lorraine, Nancy, France. They have significantly contributed to building the evidence supporting modern heart failure therapy, including MRAs, β-blockers, sodium-glucose co-transporter-2 inhibitors, and anticoagulants, as well as in major comorbid conditions in heart failure such as diabetes, hyperkalaemia, CKD, and central sleep apnoea. Zannad is past Chairman of the French Society of Hypertension, and of the European Society of Cardiology (ESC) Working Group on Pharmacology and Drug Therapy. They are also founder of the Global CardioVascular Clinical Trialists (CVCT) Forum and Workshop, a thinktank meeting dedicated to the science of clinical trials. Zannad has published more than 1,000 peer-reviewed papers, and received the Paul Milliez Award of the European Society of Hypertension (ESH), the Lifetime Achievement Award from the ESC-HFA (2017), a Eugene Braunwald Scholarship at Harvard Medical School, and the Heart Failure Society of America (HFSA) International Honorary Fellowship (2022).

References

1. Go AS et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296-305.
2. Rangaswami J et al; American Heart Association Council on the Kidney in Cardiovascular Disease and Council on Clinical Cardiology. Cardiorenal syndrome: classification, pathophysiology, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. Circulation. 2019;139(16):e840-78.
3. Atun R et al. Diabetes in sub-Saharan Africa: from clinical care to health policy. Lancet Diabetes Endocrinol. 2017;5(8):622-67.
4. Data Visualization. Diabetes prevalence in the Middle East. 2022. Available at: https://sites.aub.edu.lb/datavisualization/2022/04/15/diabetes-prevalence-in-the-middle-east/. Last accessed: 25 January 2023.
5. Metri KG et al. The deadly duo of hypertension and diabetes in India: further affirmation from a new epidemiological study. J Assoc Physicians India. 2022;70(7):11-2.
6. Barbour SJ et al. Individuals of Pacific Asian origin with IgA nephropathy have an increased risk of progression to end-stage renal disease. Kidney Int. 2013;84(5):1017-24.
7. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO 2021 clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int. 2021;99(Suppl 3):S1-87.
8. Carey RM et al; American Heart Association Professional/Public Education and Publications Committee of the Council on Hypertension; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Genomic and Precision Medicine; Council on Peripheral Vascular Disease; Council on Quality of Care and Outcomes Research; Stroke Council. Resistant hypertension: detection, evaluation, and management:

a scientific statement from the American Heart Association. Hypertension. 2018;72(5):e53-90.

9. Williams B et al; British Hypertension Society's PATHWAY Studies Group. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet. 2015;386(10008):2059-68.
10. Parthasarathy HK et al. A double-blind, randomized study comparing the antihypertensive effect of eplerenone and spironolactone in patients with hypertension and evidence of primary aldosteronism. J Hypertens. 2011;29(5):980-90.
11. Freeman MW et al; BrigHTN Investigators. Phase 2 trial of baxdrostat for treatment-resistant hypertension. N Engl J Med. 2023;388(5):395-405.
12. Schlaich MP et al; PRECISION investigators. Dual endothelin antagonist aprocitentan for resistant hypertension (PRECISION): a multicentre, blinded, randomised, parallel-group, phase 3 trial. Lancet. 2022;400(10367):1927-37.
13. Duggan S. Esaxerenone: first global approval. Drugs. 2019;79(4):477-81.
14. Ito S et al. Double-blind randomized phase 3 study comparing esaxerenone (CS-3150) and eplerenone in patients with essential hypertension (ESAX-HTN study). Hypertension. 2020;75(1):51-8.
15. Pitt B et al.; FIGARO-DKD Investigators. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. N Engl J Med. 2021;385(24):2252-63.
16. Bakris GL et al.; FIDELIO-DKD Investigators. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med. 2020;383(23):2219-29.
17. Bakris G et al; BLOCK-CKD Study Group. Effect of KBP-5074 on blood pressure in advanced chronic kidney disease: results of the BLOCK-CKD study. Hypertension. 2021;78(1):74-81.
18. Kintscher U et al. Novel non-steroidal mineralocorticoid receptor antagonists in cardiorenal disease. Br J Pharmacol. 2022;179(13):3220-34.
19. Horisberger JD, Rossier BC. Aldosterone regulation of gene transcription leading to control of ion transport. Hypertension. 1992;19(3):221-7.
20. Agarwal R et al. Steroidal and non-steroidal mineralocorticoid receptor antagonists in cardiorenal medicine. Eur Heart J. 2021;42(2):152-61.
21. Pitt B et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999;341(10):709-17.
22. Chow CP et al. Pharmacological profile of KBP-5074, a novel non-steroidal mineralocorticoid receptor antagonist for the treatment of cardiorenal disease. J Drug Res Dev. 2017;DOI:10.16966/2470-1009.137.
23. Kolkhof P et al. Finerenone, a novel selective nonsteroidal mineralocorticoid receptor antagonist protects from rat cardiorenal injury. J Cardiovasc Pharmacol. 2014;64(1):69-78.
24. Kario K et al. Effect of the nonsteroidal mineralocorticoid receptor blocker, esaxerenone, on nocturnal hypertension: a post hoc analysis of the ESAX-HTN study. Am J Hypertens. 2021;34(5):540-51.
25. Uchida HA et al; EX-DKD investigators. Efficacy and safety of esaxerenone in hypertensive patients with diabetic kidney disease: a multicenter, open-label, prospective study. Adv Ther. 2022;39(11):5158-75.
26. Ruilope LM et al; FIDELIO-DKD Investigators. Blood pressure and cardiorenal outcomes with finerenone in chronic kidney disease in type 2 diabetes. Hypertension. 2022;79(12):2685-95.
27. Agarwal R et al. Effect of finerenone on ambulatory blood pressure in chronic kidney disease in type 2 diabetes. J Hypertens. 2023;41(2):295-302.
28. Agarwal R et al.; FIDELIO-DKD and FIGARO-DKD investigators. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. Eur Heart J. 2022;43(6):474-84.
29. Bakris GL et al; Mineralocorticoid Receptor Antagonist Tolerability Study–Diabetic Nephropathy (ARTS-DN) Study Group. Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized clinical trial. JAMA. 2015;314(9):884-94.
30. Agarwal R et al. A comparative post hoc analysis of finerenone and spironolactone in resistant hypertension in moderate-to-advanced chronic kidney disease. Clin Kidney J. 2023;16(2):293-302.
31. KBP Biosciences. Efficacy and safety of KBP-5074 in uncontrolled hypertension and moderate or severe CKD (Clarion-CKD). NCT04968184. https://clinicaltrials.gov/ct2/show/NCT04968184.