Kidneys and Blood Pressure: A Key Link

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THE 61st European Renal Association (ERA) Congress took place in Stockholm, Sweden, from the 23rd–26th of May 2024. In a multidisciplinary session chaired by Mustafa Arici, Hacettepe University, Ankara, Türkiye; and Olga Barafa, University Hospital of Ioannina, Epirus, Greece, three experts discussed the crucial relationship between kidney function and blood pressure, providing recommendations for clinical practice.

CHRONIC KIDNEY DISEASE: CONTROLLING HYPERTENSION

Liffert Vogt, University of Amsterdam, the Netherlands, opened the session by emphasising the importance of blood pressure (BP) management in patients with chronic kidney disease (CKD), as outlined by the Kidney Disease, Improving Global Outcomes (KDIGO) 2024 clinical practice guidelines, which set an ambitious target for systolic BP <120 mmHg. While awareness of high BP in CKD is increasing, the proportion of patients with CKD who have their BP under control remains under 50%. Vogt brought the audience's attention to a recent trial conducted in Korea that found that greater adherence to systolic BP control within the target range was associated with a lower risk of adverse kidney events.[1]

New drugs for CKD, such as dapagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, are improving renal function, as well as lowering patient BP (average of 2.9 mmHg).[2] However, despite a better prognosis, patient BP still remains above the desired target. Vogt added that, across several recent studies, thiazide diuretics have been shown to be effective treatment approaches in patients with CKD, reducing systolic BP by an average of 14 mmHg, which is more than observed with dapagliflozin. As an add-on to traditional treatments for CKD such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, thiazide diuretics like chlorthalidone, and dietary sodium restriction (<100 mmoL/d), remain powerful options to reduce BP, in addition to lowering proteinuria and estimated glomerular filtration rate. While their effect on the long-term risk of kidney events is not as well-studied as SGLT2 antagonists or selective mineralocorticoid receptor antagonists, Vogt urged the audience to not neglect diuretics and sodium restriction as therapeutic options for patients with CKD.

Vogt then introduced results from an unpublished survey, conducted among Dutch nephrologists, where one-third of patients were reported to have a BP exceeding the recommended target, and almost half did not have an albumin-to-creatinine ratio on target. This was due to a suboptimal dose of renin-angiotensin-aldosterone system inhibitors (RAASi), or simply a lack of RAASi use. Expanding on the true burden of CKD globally, Vogt highlighted that two out of three patients with CKD are identified based on lab values, but do not have a corresponding CKD diagnosis, leading to only 60% of patients with CKD being prescribed a RAASi. Furthermore, commenting on recent CKD patient data in the UK, he explained that, in the real-world CKD population, only

0.9%, 2.2%, and 8.0% of patients would have actually been eligible for the three landmark SGLT2-inhibitor trials.[3] "What is the validity of these trials if the daily practice is completely different?" questioned Vogt. He attributed the main reason for this ineligibility to a lack of RAASi use.

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These data have crucial implications for clinical practice. Better screening strategies for CKD are needed, implementation of RAASi needs to be improved, and a greater focus should be placed on meeting the systolic BP target of <120–130 mmHg. Vogt ended his talk with perhaps a controversial approach to CKD treatment, asking whether patients with CKD will really be in need of newer classes of renoprotective agents once RAASi are adequately prescribed, and BP is controlled. "More pills does not induce more adherence," he concluded.

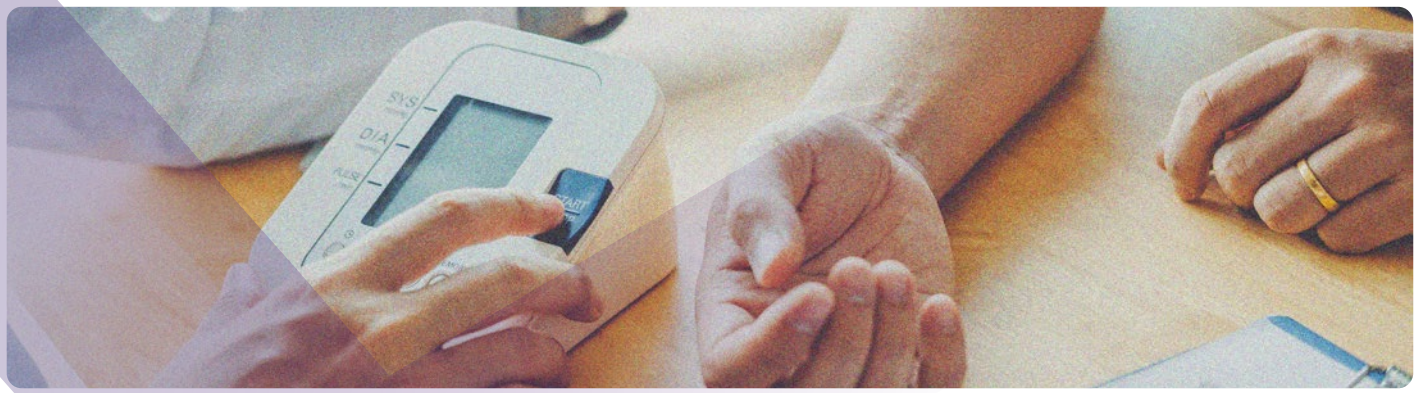
MALIGNANT HYPERTENSION: LESSONS LEARNT

Jean-Michel Halimi, University of Tours, France, stressed that 'malignant hypertension' (MH) remains a prevalent clinical issue in 2024, despite huge advances in the development of hypertensive drugs. Discussing results from his recent study, 7,769 patients were found to have hypertensive encephalopathy (HE), of which 25% died within 3 years.[4] Risk of adverse outcomes, including heart failure, ischaemic stroke, haemorrhagic stroke, cognitive impairment, and vascular dementia, among others, were all significantly higher in patients with HE compared to those without HE. "These are people who live in France, where there is no financial barrier to medical care," stressed Halimi. "We shouldn't have this issue, but this is what we have."

Halimi then spoke about thrombotic microangiopathy (TMA), which was recently shown to be part of the pathophysiology of MH. The definition of MH has expanded from elevated BP and papilledema to 'target-organ damage', including posterior reversible encephalopathy syndrome, retinopathy, acute kidney injury, TMA, and heart failure. He added that, in MH, the kidney exhibits dysregulated levels of complement, with elevated C5-b9, C3a, and C5a; and pathogenic variants of complement factors B and H.[5]

Furthermore, in a study of young patients with MH, only 7% had normal renal function at 3 years, 25% required chronic dialysis, and 52% had severe isolated nephrosclerosis.[6] Level of internal fibrosis was a crucial prognostic factor significantly associated with renal prognosis. Halimi added that, where possible, a kidney biopsy may be warranted in patients with MH.

Finally, Halimi emphasised the urgent need for new data to examine the relationship between MH and TMA. The first prospective, multicentric cohort on MH is now underway,[7] including patients with blood pressure >180/110 leading to acute damage of three target organs (heart, brain, kidney). As of May 2024, 512 patients have been recruited.



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A NOVEL TREATMENT APPROACH FOR HYPERTENSION

Kouichi Tamura, Yokohama City University, Japan, introduced a potential therapeutic option for treating hypertension-cardiovascular-kidney comorbidity. He explained that chronic overactivation of the angiotensin II receptor type 1 (AT1R) signalling system is a key challenge to overcome to achieve the healthy longevity required in an ageing society. Sustained activation of AT1R signalling leads to oxidative stress and inflammation, and subsequently a shortened life expectancy. AT1R-associated protein (ATRAP) has been identified as a specific binding protein to the C-domain of AT1R. In normal kidney cells, ATRAP is abundantly distributed in tubular epithelial cells along nephron segments. However, kidney tubule ATRAP expression decreases as renal function declines in CKD. In visceral adipose tissue, ATRAP expression also tends to be decreased in human metabolic disorders such as hypertension, Type 2 diabetes, and obesity.

Tamura explained that the current hypothesis, supported by two decades of research, is that ATRAP may exert a "functionally selective inhibition on pathological, detrimental AT1R signalling." In transgenic mice with cardiac-specific ATRAP, cardiac hypertrophy provoked by AT1R-induced hypertension was suppressed; and adipocyte-specific ATRAP enhancement suppressed visceral fat accumulation and body weight gain in mice on a high-fat diet. Furthermore, ATRAP-knockout mice exhibited exacerbation of hypertension and an increase in kidney TNF-α expression in a remnant kidney-CKD model.

Tamura provided some interesting insights into the potential avenues for implementation of ATRAP enhancement: inhibitors against microRNA-125 can increase ATRAP expression and suppress the pathological overactivation of AT1R, thus achieving organ-protective effects against hypertension and other kidney diseases. He emphasised that ATRAP is an attractive therapeutic target to tackle the comorbidities associated with an ageing population.

CONCLUSION

This comprehensive session highlighted the ongoing challenges and advances in managing hypertension and kidney disease, with speakers advocating for integrated, evidence-based strategies to enhance patient outcomes. There is a critical need to address treatment gaps in kidney disease, and BP control remains a crucial target in clinical practice. Improved screening strategies and patient adherence to medication remain a priority to reduce hypertension-related complications, morbidity, and mortality.

In the real-world CKD population, only **0.9%, 2.2%,** and **8.0%** of patients would have actually been eligible for the three landmark SGLT2-inhibitor trials

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