New therapies targeting hypertension: Implications for kidney disease

Speaker:
Johannes Stegbauer,
Germany

Panellist:
Olga Balafa,
Greece

Panellist:
Francesca Mallamaci,
Italy

Moderator:
Beatriz Fernandez Fernandez,
Spain

Hypertension is a major global public health issue and among the world's leading preventable risk factors for premature death and disability. It is associated with stroke, heart attack, heart failure, renal damage, and substantial economic costs for patients and their families, health systems and national economies. According to last year's report by the World Health Organization, the number of persons living with high blood pressure has doubled between 1990 and 2019, from 650 million to 1.3 billion, owing to population ageing and exposure to lifestyle risk factors. Even more alarming is the fact that nearly half of the affected individuals are unaware of their condition, and as many as 80% are not adequately treated.

The latest guidelines by the European Society of Hypertension (ESH) provided concise and straightforward recommendations for the management of high blood pressure. They advocate a combination therapy as initial treatment, which in chronic kidney disease (CKD) patients should include a renin-angiotensin system (RAS) blocker, calcium channel blocker and diuretic. Further actions in inadequately controlled patients with CKD include adding spironolactone or other mineralocorticoid receptor antagonist (MRA) in CKD stages 1 to 3, or thiazide/thiazide-like diuretic when an estimated glomerular filtration rate (eGFR) is below 30mL/min/1.73m^2, followed by a beta- or alpha-1 blocker, or centrally acting agent. Renal denervation is listed as a potential last-line option in cases with true resistant hypertension and eGFR greater than 40 ml/min/1.73 m^2. Several new agents, which might contribute to the treatment of resistant hypertension, are also currently in the pipeline.

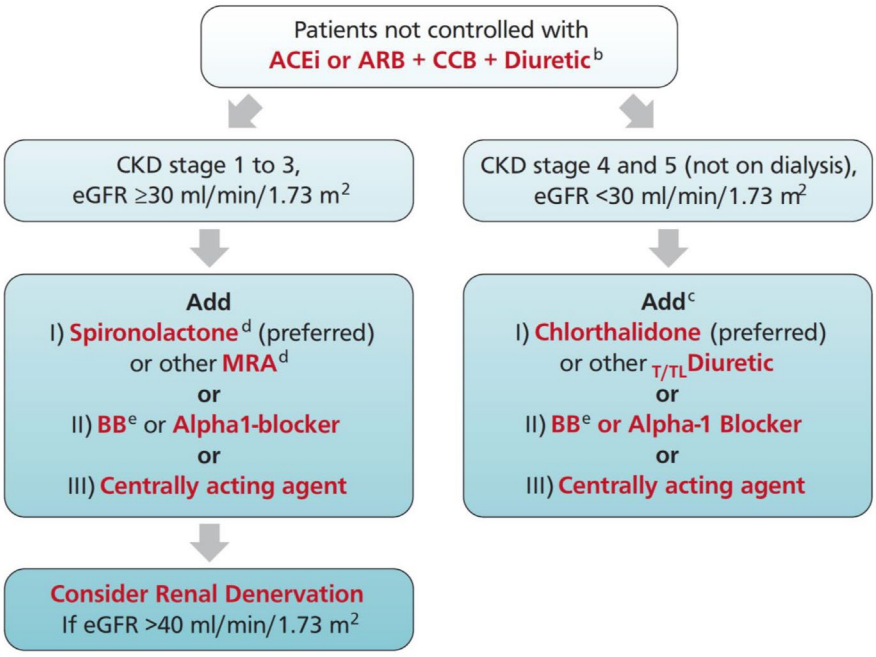


Figure 1.
Strategies for hypertension control in patients with CKD according to ESH guidelines (Mancia et al. 2023)

Endothelin antagonists

Endothelin-1 (ET-1) was discovered in 1987 as an endothelial cell-derived peptide which regulates vascular tone. Over the past three decades, it has been recognized as a multifunctional agent with cytokine-like activity contributing to almost all aspects of physiology and cell function. Endothelin acts through two types of G-protein-coupled receptors. ET_As are predominantly expressed on the smooth muscle cells of blood vessels' walls, where they act to maintain normal vascular tone. ET_Bs, on the other hand, are mainly found in the liver, renal, and pulmonary vascular endothelium, mediating vasodilatation through the release of nitric oxide and stimulation of natriuresis and diuresis. ET-1 induces a variety of biological effects in the kidney. It elicits vasoconstriction via ET_A receptors, predominantly in the efferent arteriole, and sodium and water retention via ET_B receptors in the collecting duct. It also mediates glomerular and tubular injury through inducing cytoskeletal remodelling in podocytes and loss of slit membranes. Ultimately, it acts synergistically with angiotensin-II to promote mesangial cells to release pro-inflammatory and profibrotic cytokines, stimulate cell proliferation and increase production of matrix proteins leading to glomerular sclerosis.

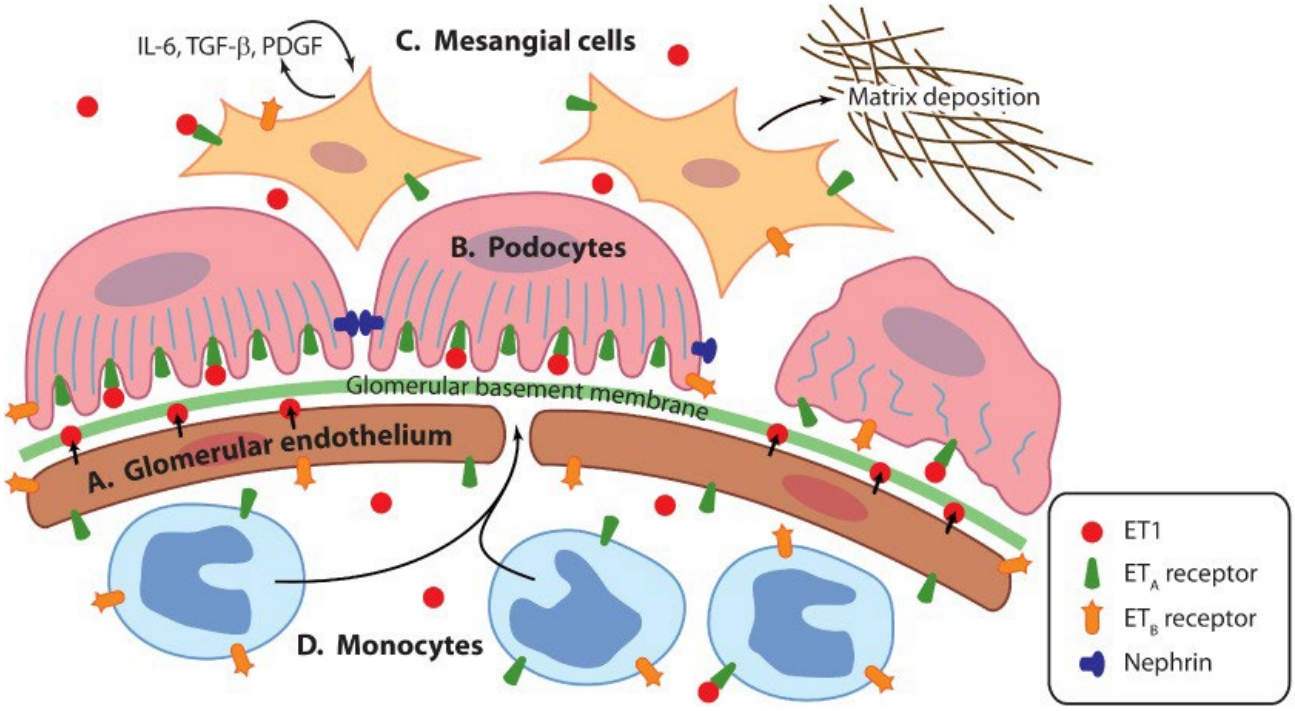


Figure 2.
Effects of endothelin 1 on glomerular structures (Dhaun et al. 2012)

ETs' role in various cardiovascular diseases led to the development of a new class of therapeutics – the endothelin receptor antagonists (ERAs). The first clinical use of ERAs was in the setting of pulmonary arterial hypertension. Bosentan was the first approved ERA for this condition, but its use is associated with hepatotoxicity and oedema as major side effects. A recently published PRECISION trial introduced a dual endothelin receptor A and B antagonist aprocitentan and examined whether its addition to a 3-agent antihypertensive regimen reduced blood pressure in patients with resistant hypertension. The study consisted of three sequential parts. Part 1 was the 4-week double-blind, randomised, and placebo-controlled part, in which patients received aprocitentan 12.5 mg or 25 mg, or placebo in a 1:1:1 ratio. Part 2 was a 32-week patient-blind part, in which all patients received aprocitentan 25 mg; and part 3 was a 12-week double-blind, randomised, and placebo-controlled withdrawal part, in which patients were re-randomised to aprocitentan 25 mg or placebo in a 1:1 ratio. About one-fifth of patients had CKD stage 3 or 4 and around one-third had microalbuminuria or albuminuria.

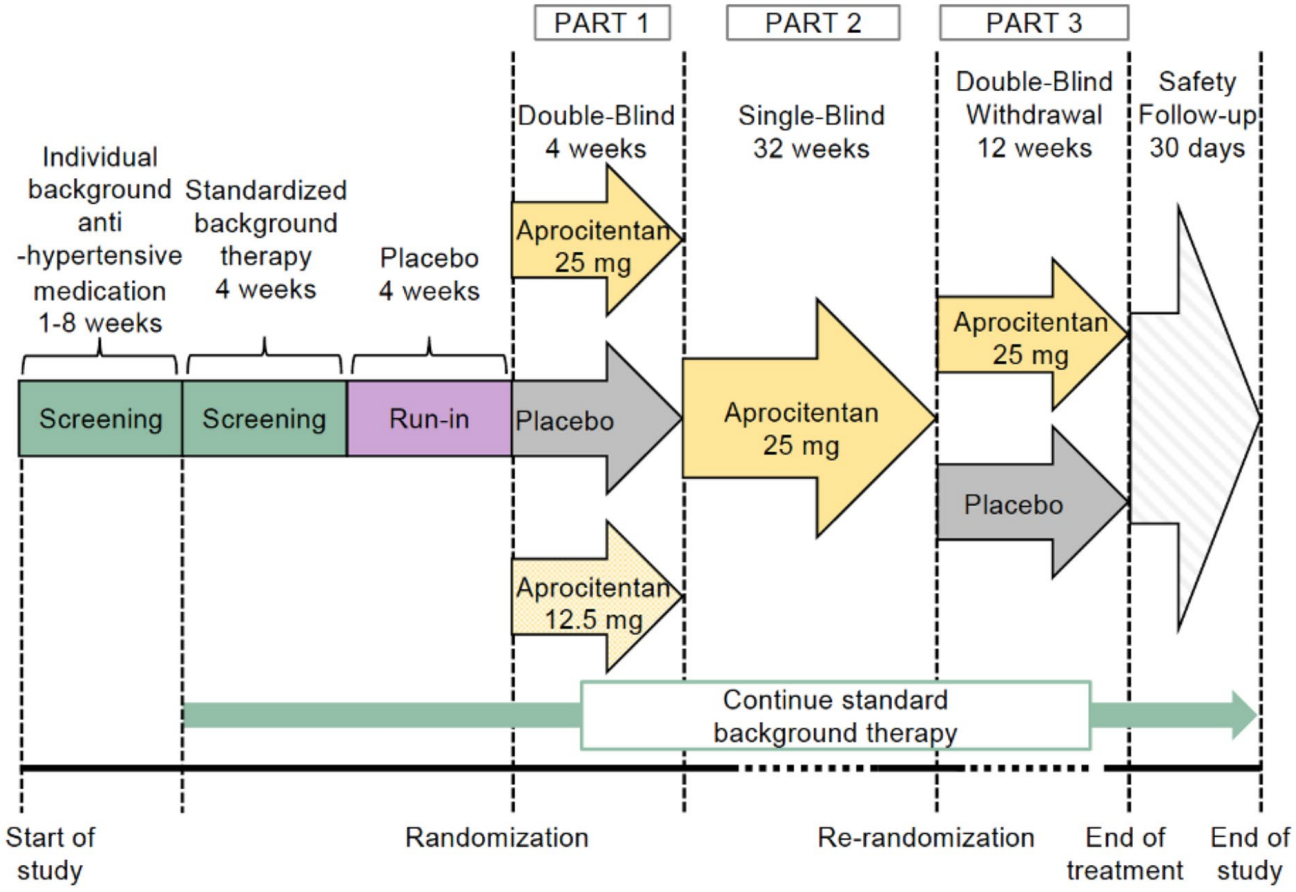


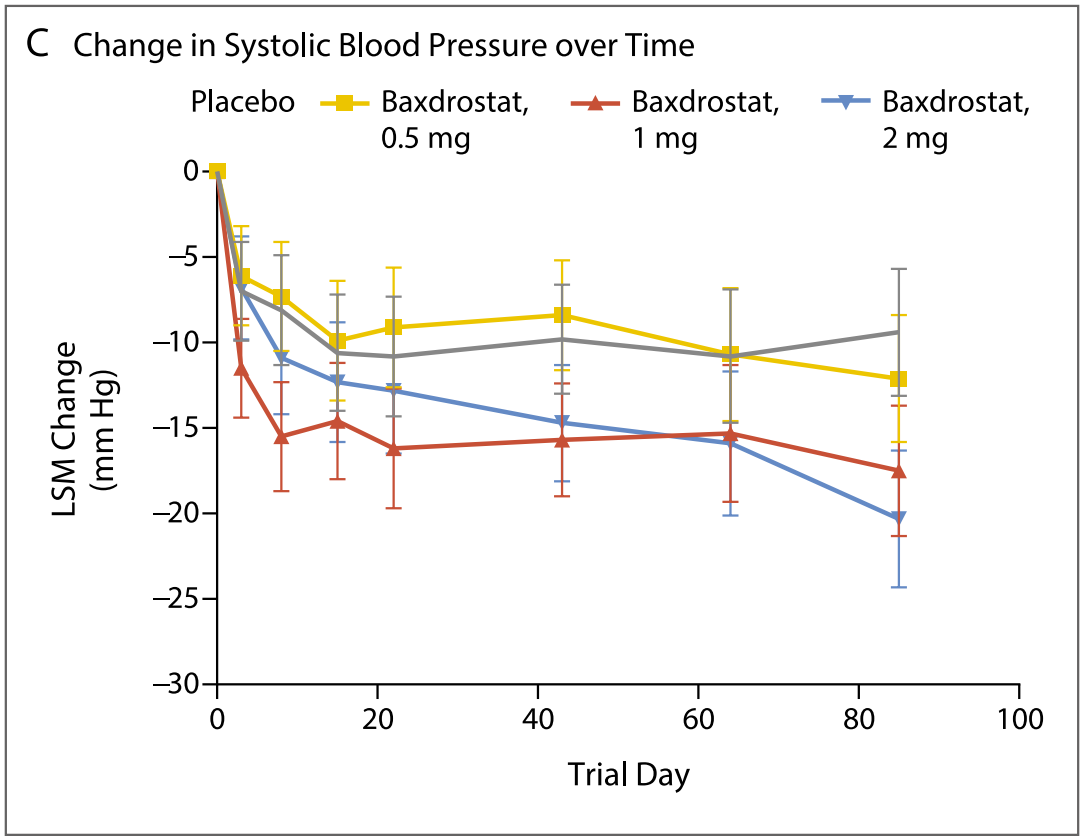
Figure 3.
The design of the PRECISION trial (Schlaich et al. 2023)

The trial found significant sustained improvement in blood pressure control over 48 weeks, coupled with a remarkable proteinuria reduction. The effect on blood pressure was consistent in all age, gender and proteinuria subgroups. The main side effect was fluid retention, which was more common in the advanced stages of CKD, and was effectively managed with diuretics in around half of the affected participants. Based on these results, it appears that aprocitentan might be a promising therapeutic in patients with resistant hypertension and a history of proteinuric CKD.

ERAs' renoprotective and antiproteinuric effects were assessed in another two trials which compared the efficacy of a dual ERA sparsentan versus irbesartan for treating focal segmental glomerulosclerosis and IgA nephropathy. Both studies established a greater reduction in proteinuria with sparsentan, albeit the effect of sparsentan on the preservation of kidney function was superior only in IgA nephropathy.

Aldosterone synthase inhibitors

Aldosterone contributes to the regulation of sodium reabsorption, water retention, and blood pressure control. It plays a major role in resistant hypertension and mediates organ damage. The earliest aldosterone antagonist, spironolactone, efficiently lowers blood pressure but is associated with gynecomastia and other sex-related adverse effects at high doses and with prolonged use. To overcome these complications, new aldosterone blockers have been developed which avoid steroid receptor cross-reactivity of classic MRAs that account for most adverse effects. The major issue in this process was to produce a highly selective suppressor of aldosterone synthase (CYP11B2) which shares 93% sequence similarity with CYP11B1 responsible for cortisol production.



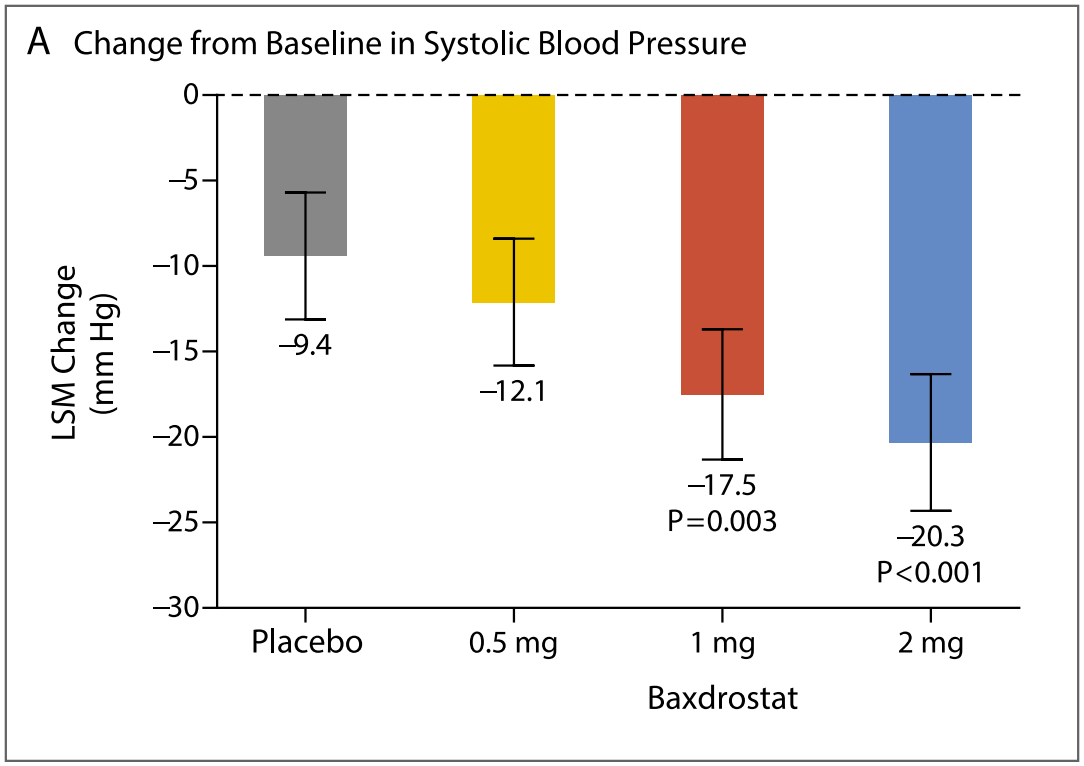


Figure 4.
Dose-dependent effects of baxdrostat in patients with resistant hypertension (Freeman et al. 2023).

Baxdrostat is a potent selective aldosterone synthase inhibitor which demonstrated promising results in phase 2 trials through remarkable dose-dependent effects in lowering systolic blood pressure in patients with resistant hypertension. Its use was not associated with any serious adverse effects so far. The incidence of treatment-associated hyperkalemia was very low and it did not recur after withdrawal and reinitiation of the drug. Lorundrostat is another aldosterone synthase inhibitor with the potential to improve the handling of treatment-resistant hypertension, as concluded in The Target-HTN phase-2 trial. It demonstrated a very robust blood pressure lowering response, particularly in overweighted patients, again with no serious adverse effects. Novel therapies might eventually bring significant improvement to a targeted approach to blood pressure management, especially in patients with resistant hypertension.

Written by Jasna Trbojevic-Stankovic.
The speaker reviewed and approved the content

KEY POINTS

1. Hypertension still represents a major treatment challenge for clinicians worldwide.
2. Endothelin is the strongest endogenous vasoconstrictor. Selective targeting of endothelin A receptors appears to improve blood pressure control and produce other beneficial effects on renal structure and function.
3. Aldosterone plays a pivotal role in resistant hypertension. Novel elective suppressors of aldosterone synthase efficiently lower blood pressure without hormonal side effects.
4. The development of novel, targeted antihypertensive treatments holds the potential to attenuate numerous complications associated with this disease, including CKD.
5. Further confirmatory studies are needed to substantiate the effects of ERAs and aldosterone synthase inhibitors in the long-term trials.

Further readings

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