



## Case Report

# Resistant to refractory hypertension: Angiotensin receptor blocker/neprilysin inhibitor to the rescue

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## ABSTRACT

Hypertension in African starts early and runs a severe course; with appalling morbi-mortality statistics. When resistant to treatment, again a phenotype more common in the African, outcome is poorer. Search for effective management has continued, ranging from novel pharmacological agents to devise therapy. The latter is invasive and beyond the reach of many needing it. Angiotensin receptor blocker/Neprilysin inhibitors are relatively new in our environment and effective in hypertensives with high salt intake and sensitivity. Since this is the situation with majority of African hypertensives, it was given to a patient with diabetes and treatment resistant hypertension of the refractory phenotype. The outcome was satisfactory hence this case report.

**Keywords:** Treatment resistance, Refractory, Hypertension, Control, Angiotensin receptor blocker/neprilysin inhibitor

## INTRODUCTION

Hypertension in the African starts early is more severe and runs an aggressive course with huge adverse health consequences. When it becomes resistant, control is poor or unattainable; the consequences of which are poorer outcomes and worse target organ damage.<sup>[1]</sup> Resistant hypertension is defined as blood pressure remaining above 140/90 mmHg despite adherence to three or more anti-hypertensives from different classes that includes a diuretic; unless contra-indicated by tolerance issues.<sup>[2]</sup> In our environment, its rate is high, 54.9% from the work of Okeahialam in 2020.<sup>[3]</sup> In the same study,<sup>[3]</sup> the extreme phenotype of resistant hypertension defined as uncontrolled hypertension with patient on five or more drugs one of which is Spironolactone was recorded in 7.1%.

The pathophysiology of resistant hypertension is poorly understood with inappropriate salt and water retention evidenced by raised brain natriuretic peptide levels reportedly demonstrated.<sup>[4]</sup> Adding Spironolactone or Chlorthalidone, a long acting thiazide effectively lowers blood pressure, failing which such cases qualify to be described as refractory hypertension.

Angiotensin receptor blocker/Neprilysin inhibitor has shown impressive blood pressure control but in trials with under-representation of blacks.<sup>[5]</sup> Given that its better performance in Asians is because of higher salt sensitivity and higher salt intake,<sup>[6]</sup> its utility in Africans becomes highly probable. Since additionally it is proposed for use in resistant hypertension,<sup>[7]</sup> one decided to avail its use to this patient whose hypertension remained uncontrolled despite use of up to five drugs one of which was Spironolactone. The response was impressive and encouraged the report

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of this case for the benefit of clinicians and patients in our environment.

## CASE REPORT

A 76-year old-lady first seen by the author in 2018 gave an 11-year history of hypertension with diabetes mellitus. She was on daily Amlodipine 10 mg, Atorvastatin 10 mg, Metoprolol 50 mg, Losartan 50 mg, Aspirin 75 mg, and Metformin 500 mg twice daily. Her blood pressure was 200/90 mmHg supine. The only change made at this visit was Amlodipine 10 mg/Indapamide 1.5 mg replacing Amlodipine 10 mg. Physical examination was insignificant. Laboratory tests were requested for cardiovascular profiling. On return 2 weeks later, electrocardiogram showed mixed atrial and ventricular ectopics, and fasting blood glucose was impaired at 7.7 mmol/L. Her Losartan was increased to 50 mg twice daily, Metformin increased to 500 mg thrice daily, and Atorvastatin was de-escalated to 5 mg daily. With this, blood glucose became controlled but blood pressure remained high at 188/66 mmHg sitting. To exclude white coat phenomenon, ambulatory blood pressure monitoring (ABPM) was requested. Overall systolic blood pressure was abnormal at 140 (>135), daytime systolic blood pressure was borderline at 139 (<140), and nighttime systolic blood pressure was abnormal at 142 (>125). Diastolic blood pressure was overall optimal at 72 (<75), daytime optimal at 75 (<80), and nighttime normal at 67 (<70). These reflect consistent isolated systolic hypertension. To confirm adherence, patient was asked to come with her drugs and adherence was ascertained. With this, Spironolactone was added to the regimen at 25 mg twice daily. This meant five drug classes two of which were diuretics; a thiazide-like diuretic in the Amlodipine/Indapamide combination and Spironolactone. Blood pressure remained at 174/68 mmHg. Spironolactone was increased thrice daily without much change as BP stood at 176/70 mmHg. At this point, Uperio brand of Sacubitril/Valsartan was introduced at 100 mg daily.

On the subsequent visits, blood pressure dropped to 143/71 mmHg, then 140/70 mmHg and in August 2021, it was 138/65 mmHg.

## COMMENTS

This patient with hypertension and diabetes satisfied the criteria for defining the extreme phenotype of resistant hypertension known as refractory hypertension. Risk factors for refractory hypertension include black race and diabetes mellitus among others. The patient satisfied these two criteria. The sustained poor control exposes them to worse outcomes related to target organ damage. Having availed her of ABPM and confirmed medication adherence, the diagnosis of refractory hypertension was no longer in doubt.<sup>[8]</sup> Replacing

her Losartan with the Valsartan/Sacubitril combination got her blood pressure normalized.

Natriuretic peptides affect salt and water balance profoundly, apart from their ability to inhibit the renin-angiotensin-aldosterone system (RAAS) and sympathetic drive.<sup>[9]</sup> Neprilysin catalyzes the metabolism of these peptides and with its inhibition, the levels of the peptides rise; as well as degradation of Angiotensin II.<sup>[10]</sup> When RAAS blockade is added, a synergistic effect for better blood pressure control is produced.

The result here is encouraging. Given the salt sensitivity of our hypertension, and the inappropriate sodium and fluid retention in these patients, it is recommended that Neprilysin inhibitor/Angiotensin receptor blocker combination be considered when managing refractory hypertension.

## CONCLUSION

In conclusion, Neprilysin inhibitor/angiotensin receptor blocker combination should be considered when hypertension becomes resistant or refractory to treatment.

## Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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## Conflicts of interest

There are no conflicts of interest.

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