ADVANCES IN RESISTANT AND REFRACTORY HYPERTENSION

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I DEFINITIONS: RESISTANT VS. REFRACTORY HYPERTENSION

- **Resistant Hypertension (RH):** Blood pressure (BP) that remains above **130/80 mmHg** (or 140/90 mmHg depending on guidelines) despite the concurrent use of **three antihypertensive agents** of different classes (typically an ACEi/ARB, a Calcium Channel Blocker, and a Diuretic) at maximally tolerated doses.
- **Refractory Hypertension:** A more severe phenotype in which BP remains uncontrolled despite at least **five different antihypertensive agents**, including a mineralocorticoid receptor antagonist (MRA) and a long-acting thiazide-like diuretic.

II PHARMACOLOGICAL ADVANCES

- **Non-Steroidal Mineralocorticoid Receptor Antagonists (Finerenone):**
  - **Mechanism:** Unlike Spironolactone, Finerenone is non-steroidal and more selective, with a lower risk of gynecomastia.
  - **Evidence:** The **FIDELIO-DKD** and **FIGARO-DKD** trials demonstrated cardiorenal protection in type 2 diabetes with CKD, with only modest BP lowering; it is not licensed as an antihypertensive.
  - **Dual Endothelin Receptor Antagonists (Aprocitentan):**
  - **Mechanism:** Inhibits endothelin-1 (blocking both ETA and ETB receptors), a potent vasoconstrictor elevated in resistant hypertension.
  - **Evidence (PRECISION Trial):** Showed that Aprocitentan significantly reduced BP in patients with resistant hypertension when added to standardized background therapy (FDA approved in 2024).
  - **Aldosterone Synthase Inhibitors (Baxdrostat):**
  - **Mechanism:** Directly inhibits the enzyme responsible for aldosterone synthesis rather than blocking the mineralocorticoid receptor.
  - **Evidence (BrigHTN Trial):** Demonstrated dose-dependent reductions in systolic BP in patients with resistant hypertension; the Phase III **BaxHTN** trial (*NEJM* 2025) confirmed a placebo-adjusted SBP fall of about 9 to 10 mmHg.

III DEVICE-BASED THERAPIES

- **Renal Denervation (RDN):**
  - **Technique:** Radiofrequency- or ultrasound-based catheter ablation of the sympathetic nerves in the renal arteries.
  - **Current Status:** Following the **SPYRAL HTN-ON MED** and **RADIANCE II** trials, RDN is a **Class IIb** recommendation (ESC 2024) for patients with true resistant hypertension who are intolerant of or fail polypharmacy.
  - **Carotid Baroreceptor Activation Therapy (BAT):**
  - **Technique:** An implanted device (Barostim) that electrically stimulates the carotid baroreceptors, lowering central sympathetic outflow and increasing parasympathetic activity.
  - **Evidence:** Evidence comes mainly from the **Rheos Pivotal Trial** and registries (BeAT-HF studied heart failure, not hypertension); it is not routinely recommended.

IV SUMMARY OF LANDMARK TRIAL EVIDENCE

Trial Name	Intervention / Agent	Key Clinical Finding & Status
PATHWAY-2	**Spironolactone** vs. Bisoprolol or Doxazosin	Confirmed **Spironolactone** as the most effective fourth-line agent for resistant hypertension
PRECISION	**Aprocitentan** (Dual ERA)	Significant BP reduction when added to standardized background therapy in resistant HTN
BrigHTN	**Baxdrostat** (Aldosterone synthase inhibitor)	Dose-dependent systolic BP reduction in resistant hypertension
SPYRAL HTN-ON MED & RADIANCE II	**Renal Denervation (RDN)** (RF & Ultrasound)	Proved the 24-hour "Always-On" BP reduction effect independent of medication adherence
SYMPLICITY HTN-3 (Long-Term)	Multi-electrode RF Renal Denervation	Neutral at 6 months, but 36-month follow-up showed larger, durable BP reductions with RDN vs sham

V THE INDIAN CLINICAL CONTEXT

- **Biochemical Adherence Testing:** Biochemical screening (urine or blood testing) for drug adherence is advocated before labeling a patient as having true refractory hypertension.
- **High Dietary Salt Sensitivity:** Given the high salt intake in the Indian diet, long-acting **Chlorthalidone** is preferred over Hydrochlorothiazide as the thiazide-like diuretic of choice.
- **Role of Renal Denervation:** Where long-term drug adherence is compromised by heavy pill burden, RDN is considered in high-risk patients with resistant hypertension.

KEY REFERENCES

- **Williams B, MacDonald TM, Morant S, et al. (PATHWAY-2 Investigators):** Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2), *The Lancet*.
- **Schlaich MP, Bellet M, Weber MA, et al. (PRECISION Investigators):** Dual endothelin antagonist aprocitentan for resistant hypertension (PRECISION), *The Lancet*.
- **Freeman MW, Halvorsen YD, Marshall W, et al. (BrigHTN Investigators):** Phase 2 Trial of Baxdrostat for Treatment-Resistant Hypertension, *New England Journal of Medicine*.