disease, and cardiovascular death than adults with hypertension without resistance to treatment.[21-23] Evaluation of resistant hypertension requires exclusion of pseudoresistance, including inaccurate BP measurement (Section 3.1.3, "Out-of-Office BP Monitoring"), use of interfering medications (Section 5.2.6, "Medication Interactions"), white-coat hypertension via out-of-office BP monitoring (Sections 3.1.3, "Out-of-Office BP Monitoring," and 3.2.2, "White-Coat Hypertension and Masked Hypertension, and White-Coat Effect and Masked Uncontrolled Hypertension"), and medication nonadherence (Section 5.2.5, "Antihypertensive Medication Adherence Strategies"). Routine measurement of out-of-office BP is an important component of resistant hypertension management as both home BP and 24-hour ABPM are shown to be superior to office BP in predicting cardiovascular events.[24,25] Screening for secondary hypertension (Section 3.2.3, "Secondary Forms of Hypertension") should be performed because, depending on the specific cause, these conditions require a distinct management strategy.

RDN is an additional option to consider in managing resistant hypertension. In the absence of antihypertensive medications, RDN induced a reduction in 24-hour or daytime ambulatory SBP by 4 to 6 mm Hg during a follow-up duration of 2 to 3 months.[26-28] In the presence of a 2- to 5-agent antihypertensive drug regimen or resistant hypertension, the efficacy of newer-generation devices appears variable. While some trials showed a small but significant reduction in 24-hour ambulatory SBP by 3 to 5 mm Hg over the sham arm,[13,14] others failed to reach their primary endpoint.[29-31] Although broader indications are approved for the RDN devices by the FDA, given the relatively short duration of follow-up in clinical trials with modest BP-lowering effects and the absence of CVD outcome trials, RDN should not be considered as a curative therapy for hypertension or full replacement for antihypertensive drugs.

Recommendation-Specific Supportive Text

1. Approximately 20% of adults with hypertension reported regular use of over-the-counter or nonprescription medications that may directly raise BP or interfere with antihypertensive drug efficacy, such as NSAIDs or nasal decongestants (**Table 17**).[2] These medications are associated with uncontrolled BP and should be reviewed during evaluation of patients with resistant hypertension.[2] Some prescription drugs are known to elevate BP and should be replaced with alternative agents that avoid hypertensive side effects, if possible; however, in some settings, such as the treatment of malignant diseases, the contributing medication should be continued if hypertension can be controlled. Secondary hypertension is more common among adults with resistant hypertension, particularly primary aldosteronism, OSA, renal parenchymal disease, and renovascular disease.[1] Screening for secondary hypertension is discussed in Section 3.2.3 ("Secondary Forms of Hypertension").
2. Antihypertensive drug therapy should start with a combination of an ACEi or ARB, a CCB, and a diuretic.[15] Replacing thiazide-type diuretics (eg, HCTZ or bendroflumethiazide) with thiazide-like diuretics (eg, chlorthalidone and indapamide) may offer additional BP reduction[32,33] and cardiovascular protection among patients with previous MI or stroke. [34] RCTs have shown that addition of spironolactone (25-50 mg/day) as the fourth drug reduced home and 24-hour SBP by 6.6 to 8.7 mm Hg when compared with placebo in patients with resistant hypertension and eGFR ≥45 mL/min/1.73 m^2.[6,7] The reduction in BP was greater than with addition of doxazosin or bisoprolol.[6] The magnitude of reduction in 24-hour systolic and diastolic BP was greater with spironolactone than clonidine in a separate clinical trial.[8] Nevertheless, 4% to 40% of adults with resistant hypertension cannot tolerate spironolactone due to hyperkalemia or antiandrogenic side effects.[35-38] Eplerenone, a more selective steroidal MRA that avoids the antiandrogenic side effects but may cause hyperkalemia, is a potential alternative to spironolactone, but RCTs have not demonstrated reduction of home BP or 24-hour BP at doses between 25 and 100 mg daily when compared with placebo, and effective treatment may require higher dosages.[39-41] Use of nonsteroidal MRA for treating resistant hypertension in patients with moderate to advanced CKD has not been tested in a clinical trial but may be considered in selected patients with close monitoring of serum potassium.
3. When spironolactone or eplerenone are not tolerated due to side effects or cost, amiloride (10-20 mg) has been shown to be as effective as spironolactone in adults with resistant hypertension.[42] Other alternative fourth- and fifth-line drug therapies include BBs, alpha blockers, central sympatholytic drugs, and direct