expected to decrease during sleep by 10%–20% relative to daytime BP.[878] Night-time dipping patterns are classified into four groups:[879,880]

- **Inverse dipping (riser):** nocturnal increase in BP (night-to-day ratio of >1.0).
- **Non-dipper:** reduced night-time BP dip of <10% (or night-to-day ratio of >0.9 and ≤1.0).
- **Normal dipping:** fall in night-time BP of >10% and <20% (or night-to-day ratio of 0.8 to 0.9).
- **Extreme dipping:** marked fall in night-time BP of >20% (or night-to-day ratio of <0.8).

Patients with nocturnal hypertension may be dippers or non-dippers. Of note, the long-term reproducibility of dipping patterns appears to be low.[881,882]

9.12.2. Epidemiology

Nocturnal hypertension has been observed in up to half of patients with hypertension,[883–886] and is associated with increased HMOD,[883] impaired renal function, and diabetes mellitus.[887] Nocturnal hypertension appears to be more prevalent in black[888–890] and Asian[891,892] populations. Masked uncontrolled hypertension, which occurs in 30% of patients treated for hypertension, is more often due to poorly controlled nocturnal BP than daytime BP on ABPM.[893]

Environmental factors, including sleep duration and higher humidity,[894] nocturia,[895] OSAS,[896] obesity, high salt intake in salt-sensitive patients,[897] orthostatic hypotension, autonomic dysfunction, CKD,[898–900] diabetic neuropathy/diabetes,[901] and old age[62] are associated with non-dipping. Moreover, nocturnal hypertension and absent night-time dipping pattern are more common in secondary hypertension.[902,903]

9.12.3. Night-time blood pressure as a cardiovascular disease risk factor

Nocturnal hypertension is a risk factor for adverse CVD events,[904] cerebrovascular disease, including stroke,[905] and cardiovascular mortality.[891,906,907] Night-time BP may provide more prognostic information than daytime BP, perhaps as it is less dependent on physical activities. Non-dipping[908–910] and reverse dipping (nocturnal rise in BP) may also be associated with increased CVD risk.[62,910–913] A nocturnal rise in BP is associated with an increased risk of dementia and Alzheimer's disease in older men.[914] There is also some evidence that extreme dipping, particularly in untreated patients, is associated with an increased risk for CVD events.[35,886]

9.12.4. Treatment of nocturnal hypertension

There is no reliable evidence that BP-lowering medication should be routinely dosed at bedtime. The diurnal timing of drug administration is discussed in *Section 8.3.4*. In patients with secondary hypertension, the underlying cause (OSAS, primary aldosteronism) should be treated as discussed in *Section 9.14*.

9.13. Resistant hypertension

9.13.1. Definition of resistant hypertension

Resistant hypertension is defined as BP remaining above goal despite three or more BP-lowering drugs of different classes at maximally tolerated doses, of which one is a diuretic (*Table 11*).[915] Resistant hypertension should be managed at specialized centres with the expertise and resources to exclude pseudo-resistant hypertension (adherence testing) and causes of secondary hypertension.[916]

9.13.2. Non-pharmacological interventions

The Treating Resistant Hypertension Using Lifestyle Modification to Promote Health (TRIUMPH) trial demonstrated significant clinic and ambulatory BP reductions in patients with resistant hypertension participating in a 4-month lifestyle intervention comprising diet and exercise interventions delivered within a cardiac rehabilitation programme.[917]

9.13.3. Pharmacological interventions

BP-lowering treatment of resistant hypertension with single-pill combinations is recommended to reduce the pill burden, thereby increasing drug adherence and persistence.[492]

As resistant hypertension often, and especially in CKD,[918] represents a state of salt retention and volume expansion secondary to relative aldosterone excess,[516,919,920] BP control may be improved by switching hydrochlorothiazide to long-acting thiazide-like diuretics, such as chlorthalidone.[921,922] However, a recent trial of chlorthalidone vs. hydrochlorothiazide—which probably included a sizeable proportion of adults with resistant hypertension—did not demonstrate any difference in systolic BP or CVD outcomes between the two medications. In the subgroup of patients with prior CVD, there was a strong trend of benefit with chlorthalidone on CVD outcomes.[447] Of note, the risk of hypokalaemia was higher in the chlorthalidone group than in the hydrochlorothiazide group.[447] In patients with eGFR < 30 mL/min/1.73 m^2, an adequately up-titrated loop diuretic is necessary to define resistant hypertension.

Most patients with resistant hypertension require the addition of non-first-line BP-lowering drugs (*Figure 22*). Of these, low-dose spironolactone (25–50 mg daily) should be considered first.[459,515,923–925] In patients with resistant hypertension and type 2 diabetes, spironolactone (25–50 mg daily) reduced BP and albuminuria.[926] The use of spironolactone can be precluded by limited tolerability due to anti-androgenic side effects resulting in breast tenderness or gynaecomastia (in about 6%), impotence in men, and menstrual irregularities in women.[927] The efficacy and safety of spironolactone for treating resistant hypertension have not yet been established in patients with significant renal impairment. Moreover, spironolactone, especially in addition to RAS inhibitors, increases the risk of hyperkalaemia.[927,928] Therefore, spironolactone should be restricted to patients with an eGFR of ≥30 mL/min/1.73 m^2 and a plasma potassium concentration of ≤4.5 mmol/L.[459] Steroidal MRAs are contraindicated in patients with an eGFR of <30 mL/min/1.73 m^2. Serum electrolytes and kidney function should be monitored soon after initiation and frequently thereafter. In patients with resistant hypertension and CKD (eGFR of 25–45 mL/min/1.73 m^2), the oral potassium binder patiromer enabled more patients to continue treatment with spironolactone.[929]

If spironolactone is not tolerated due to anti-androgen side effects, eplerenone may be used. If eplerenone is used, higher doses (i.e. 50–200 mg daily) and twice-daily dosing may be necessary to achieve a BP-lowering effect.[503] Of note, eplerenone is not licensed for hypertension treatment in many countries.

When not already prescribed for a compelling indication, beta-blockers should be considered in the treatment of resistant hypertension, though their BP-lowering effects appear to be less potent than spironolactone in the setting of resistant hypertension.[459]

Amiloride and clonidine have data suggesting they are as effective as spironolactone for BP lowering, though they lack outcomes data. A non-exhaustive list of additional medications sometimes used for BP-lowering purposes includes other centrally acting BP-lowering medications (e.g. methyldopa), hydralazine, aliskiren, minoxidil, triamterene, and loop diuretics (*Figure 22*).[515,516] As noted earlier, minoxidil use is often limited by side effects.