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# Usefulness of measuring the serum concentration of antihypertensive drugs in uncontrolled hypertension

PERSPECTIVES

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## One-third of the adult population in Norway has hypertension. Despite receiving lifestyle advice and drug therapy, only half achieve the recommended blood pressure range. Measurements of serum drug concentrations can reveal poor medication adherence and can be used to personalise treatment.

The fact that half of patients with hypertension do not achieve their blood pressure goal despite receiving lifestyle advice and drug therapy is concerning (1–3). Persistent hypertension is associated with the development of diseases affecting the heart, arteries, brain and kidneys. Hypertension is the leading cause of years of life lost globally (4).

Various factors affect blood pressure, and monitoring techniques should therefore be standardised. In 2023, the European Society of Hypertension (ESH) published an updated version of the Guidelines for the Management of Arterial Hypertension, in which the definition of hypertension is based on the various methods of blood pressure monitoring, such as at a doctor's office, ambulatory (24-hour) and at home, where patients measure their own blood pressure (5), see Table 1.

**Table 1**

Definition of hypertension based on different ways of measuring average blood pressure. The Journal of Hypertension has consented to reproduction of this table (5).

| Method | Systolic blood pressure (mmHg) | | Diastolic blood pressure (mmHg) |
|---|---|---|---|
| **Office BP, standardised monitoring** | ≥ 140 | and/or | ≥ 90 |
| **24-hour ambulatory BP** | | | |
| 24-hour period | ≥ 130 | and/or | ≥ 80 |
| Daytime | ≥ 135 | and/or | ≥ 85 |
| Nighttime | ≥ 120 | and/or | ≥ 70 |
| **Home BP** | ≥ 135 | and/or | ≥ 85 |

The guidelines provide recommendations for treating hypertension with lifestyle advice and medication (5) (Figure 1). The roughly 50 % of patients who do not achieve their blood pressure goal (1–3) are defined as having uncontrolled hypertension. This may be due to various factors: improperly performed blood pressure monitoring, undiagnosed secondary hypertension,

non-adherence to lifestyle advice, too few or insufficient doses of medications, unsuitable choice of medication, non-adherence to medication and/or ineffective pharmacotherapy. About 5 % of patients with hypertension have true resistant hypertension, defined as failure to control blood pressure despite taking maximum doses of three recommended medications, including a diuretic (5).

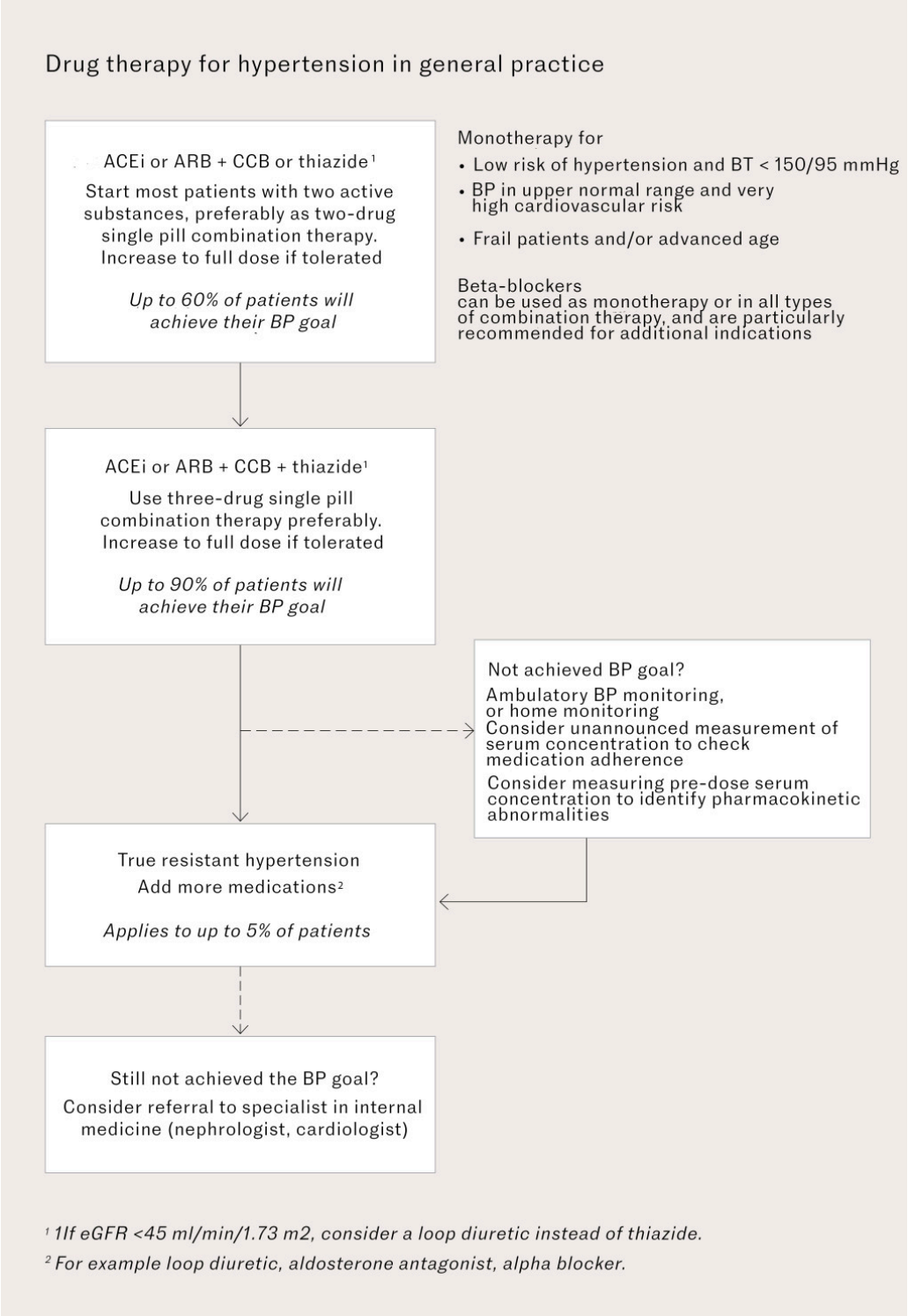


**Figure 1** Recommended as first-line agents for the treatment of hypertension in the revised ESH guidelines. The figure has been slightly adapted and reproduced with the permission of the Journal of Hypertension (5). The figure is supplemented with our recommendations on the role of therapeutic drug monitoring in patient follow-up, in line with the recommendations in the guidelines. More detailed information on indications for assessing medication adherence can be found in the text of the article.

ACEi = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker, CCB = dihydropyridine calcium channel blocker, BP = blood pressure.

## Medications in blood pressure management

The guidelines recommend the use of two medications for most patients with hypertension, preferably as a two-drug single pill combination, to ensure adherence and achieve a synergistic effect on blood pressure (5), see Figure 1. Angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB), dihydropyridine calcium channel blockers (CCB) and thiazide diuretics are the recommended medications. Beta-blockers are also first-line treatment but are only recommended for use if there are additional indications, such as coronary disease, heart failure or tachyarrhythmias. In the case of resistant hypertension, a loop diuretic, potassium-sparing diuretic and/or alpha-blocker can be used in addition (5).

The various drug groups have well-documented effects on lowering blood pressure (6), morbidity and mortality. The health benefits of treatment are related to the reduction in blood pressure and less so to the specific medications used (5). However, a report from 2023 shows that the effect on systolic blood pressure of four different medications given to the same patient differed by up to 4.4 mmHg. This suggests that personalised drug therapy may improve treatment efficacy (7).

## Pharmacological reasons for uncontrolled blood pressure

The lack of expected effect of medications on blood pressure can be due to pharmacokinetic and pharmacodynamic factors specific to the individual patient. Pharmacokinetic variation is caused by differences in the absorption, distribution, metabolism and excretion of a drug, which in turn will alter the concentration of the drug at the site of action, causing a changed drug response. Pharmacodynamic variation is caused by changes in the effect/mechanism of action of a drug without changing the serum concentration.

> ***«The lack of expected effect of medications on blood pressure can be due to pharmacokinetic and pharmacodynamic factors specific to the individual patient»***

Pharmacokinetic and pharmacodynamic variations can both be due to age, sex, medical history, altered organ function, drug interactions, environmental factors and pharmacogenetic factors specific to the patient. Lack of efficacy can also be due to a failure to adequately intensify or up-titrate treatment (referred to as 'physician inertia' in the ESH guidelines), or prescribing medications that are not suitable for the patient.

## Are patients taking their medicine?

Various studies report that 10–30 % of patients with hypertension may have a low medication adherence (2, 8, 9). This could be due to adverse effects of their medication, a feeling that there is no point in taking the medicine, forgetfulness and poor routines, cognitive impairment or other illnesses that affect a patient's ability to follow a treatment regimen. For most patients, hypertension is asymptomatic, and this is associated with lower medication adherence compared to symptomatic conditions.

> ***«For most patients, hypertension is asymptomatic, and this is associated with lower medication adherence compared to symptomatic conditions»***

There are various ways to assess medication adherence: talking to the patient, directly observed therapy followed by blood pressure measurement, checking prescription refill rates and counting pills, using an electronic pill dispenser and measuring the concentration of the medication in serum or urine (10). The latter is considered the most objective and is also feasible in clinical practice.

Analyses to measure serum concentrations of antihypertensive drugs are available at St Olav's Hospital in Trondheim and at Oslo University Hospital (11, 12). The working group of the ESH recommends measuring serum or urine concentrations of antihypertensive drugs in patients who do not achieve their blood pressure goal (5, 13).

## Measuring serum levels

The doctor can establish whether the patient is actually taking their medication and if the drug concentrations are in the expected range by measuring the serum level of antihypertensive drugs and comparing the results with the patient's medication list (14) (Table 2). The results can be assessed in conjunction with blood pressure readings and other clinical findings. The pharmacokinetic properties of antihypertensive drugs are well known. For example, altered kidney function, drug interactions and slow or fast metabolism due to changed pharmacogenetics can result in abnormal drug concentrations.

**Table 2**

Pharmacokinetic properties and dose-adjusted reference ranges for the most frequently prescribed antihypertensive drugs. Medications with low renal elimination are mainly excreted via bile/faeces. For four of the drugs, we measure the metabolite of the parent substance. A blood sample for determining serum concentration is taken before the morning dose at achieved steady-state concentration (after five half-lives). When using recommended doses, the result can be compared with the reference range in the far

right column. A blood sample to check medication adherence can be taken at any time during the dosing interval, and a result below the lower limit of the reference range can be used as an indication of low adherence.

| Antihypertensive drugs | Half-lives (t)[1] | Metabolism[2] | Percentage of renal secretion[2] (parent substance + metabolites) | Dose-related reference range (nmol/L)[2] |
|---|---|---|---|---|
| Alpha-blockers | | | | |
| Doxazosin (extended release) | 15–19 | CYP 3A4, (2D6, 2C9) | 9 | 5–80 |
| Beta-blockers | | | | |
| Atenolol | 6–9 | None | 50 | 75–750 |
| Bisoprolol | 10–12 | CYP 2D6, (3A4) | 100 | 10–200 |
| Carvedilol | 7–10 | CYP 2D6, 2C9 etc. | < 2 | 2.5–50 |
| Labetalol | 5–8 | Conjugation | 65 | 50–1 000 |
| Metoprolol (extended release) | 3–4 | CYP 2D6 | 95 | 10–500 |
| Calcium channel blockers | | | | |
| Amlodipine | 35–50 | CYP 3A4/5 | 70 | 10–40 |
| Diltiazem (extended release) | 4–10 | CYP 3A4, (2D6) | 70 | 100–500 |
| Lercanidipine | 8–10 | CYP 3A4 | 50 | 0.20–5 |
| Nifedipine (extended release) | 6–11 | CYP 3A4 | 80 | 20–150 |
| Verapamil (extended release) | 4–12 | CYP 3A4 etc. | 75 | 40–400 |
| Angiotensin-converting enzyme inhibitors | n | | | |
| Enalaprilat (metabolite of enalapril) | 11 | Carboxylesterase | 60 | 10–300 |
| Lisinopril | 12 | None | 100 unchanged | 10–300 |
| Ramiprilat (metabolite of ramipril) | 13–17 | Carboxylesterase | 60 | 4–60 |
| Angiotensin II receptor blockers | | | | |
| Irbesartan | 11–15 | Conjugation | 20 | 300–3 000 |
| Candesartan | 9 | CYP 2C9 (low proportion) | 30 | 15–200 |

| Antihypertensive drugs | Half-lives (t)[1] | Metabolism[2] | Percentage of renal secretion[2] (parent substance + metabolites) | Dose-related reference range (nmol/L)[2] |
|---|---|---|---|---|
| Losartan carboxylic acid (metabolite of losartan) | 6–9 | CYP 2C9, 3A4 (low proportion) | 35 | 30–350 |
| Telmisartan | 24 | Conjugation | < 1 | 8–80 |
| Valsartan | 6 | CYP 2C9 (low proportion) | 13 unchanged | 300–4000 |
| Thiazide diuretics | | | | |
| Bendroflumethiazide | 3 | 70 % (unknown enzymes) | 30 unchanged | 1.5–30 |
| Hydrochlorthiazide | 9–13 | None | 60–100 unchanged | 15–300 |
| Aldosterone antagonists | | | | |
| Eplerenone | 3–6 | CYP 3A4 | 70 | 3.5–350 |
| Canrenone (metabolite of spironolactone) | 9–24 | Unknown enzymes | 60 | 15–300 |

[1]Data from Thorstensen et al. (12)

[2]Data from Rognstad et al. (14)

The general idea with therapeutic drug monitoring is that if the serum concentration level is within the reference range, therapeutic effects can be expected. If the level is below this range, the dose can be increased, and if it is above, the dose can be reduced. Serum measurements can therefore serve as an aid for optimising the dosage and for choosing the most suitable medication for the patient. Measuring serum concentrations of antihypertensive drugs can help doctors identify and improve low medication adherence and adjust concentrations to dose-related reference ranges (2, 8, 9, 12, 15–17). However, more research is needed to determine whether such measurements have an effect on blood pressure, although some studies do suggest that they can help to control blood pressure (18).

## Monitoring uncontrolled hypertension

Adherence to lifestyle advice and drug therapy are specifically addressed in the 2023 ESH guidelines (5). Assessment of medication adherence is recommended at all blood pressure checks, and particularly before changing medication, in secondary hypertension investigations and when true resistant hypertension is suspected. Adherence should also be assessed in patients with

only a slight reduction in blood pressure despite combination therapy with two active ingredients. We recommend measuring drug concentrations to assess adherence in patients with uncontrolled hypertension (Figure 1) (19).

In order to ensure that analysis results present a representative picture of medication adherence, unannounced blood sampling is performed during routine check-ups. Blood sampling for testing can be carried out at any time within the dosing interval. Information about the medication, dose, start/dose change date, date/time of last intake and blood sampling must be entered on the requisition form. To assess medication adherence over time, multiple blood samples must be taken, as most antihypertensive drugs have a relatively short half-life (Table 2).

> ***«In order to ensure that analysis results present a representative picture of medication adherence, unannounced blood sampling is performed during routine check-ups»***

In addition to identifying any non-adherence, serum concentration measurements can reveal pharmacokinetic abnormalities, which the doctor then takes into account in any potential dose adjustments or changes to medication (19). In such cases, the blood sampling for testing should be carried out before the morning dose is taken, and the test result should be compared with dose-related reference ranges (Table 2). Here too it is important to specify the medication, dose, start/dose change date, date/time of last intake and blood sampling on the requisition form.

## Costs

The cost of cardiovascular medications, which are largely used to treat hypertension, was approximately NOK 1 billion in Norway in 2020 (20). Hypertension often requires lifelong medication, and inadequate treatment response also incurs high costs due to increased morbidity and the reduced capacity to work that is often entailed. Ensuring effective drug therapy is therefore important from both a medical and socioeconomic perspective (1). The Norwegian Health Economics Administration's rate for performing this type of therapeutic drug monitoring is currently around NOK 680. Patients typically use two medications and need at least one blood pressure check each year. The amount that a patient with uncontrolled hypertension pays for therapeutic drug monitoring is small compared to the actual cost. Few cost-benefit analyses have been conducted on antihypertensive drug monitoring, but one study concluded that there is a likely socioeconomic benefit (21).

## Conclusion

Many patients with hypertension do not achieve their blood pressure goal, often due to low medication adherence. Serum concentration measurements of antihypertensive drugs can indicate whether a patient is taking their medication as prescribed and reveal pharmacokinetic abnormalities that might explain a reduced drug response. In line with the updated ESH guidelines, we recommend that this type of therapeutic drug monitoring is performed for patients with uncontrolled hypertension, including at blood pressure checks in first-line services.

*The authors Opdal, Rognstad, Halvorsen, Mo, Gustavsen, Larstorp and Søraas have participated in the national hypertension study, IDA-studien.no.*

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