CORRESPONDENCE

Arterial Hypertension

by Prof. Dr. med. Jens Jordan, Prof. Dr. med. Christine Kurschat, and Prof. Dr. med. Hannes Reuter in issue 33–34/2018

Gynecological Causes Should Not Be Forgotten

With the onset of menopause, the vasodilatory effects of estrogen fail: a causal treatment with a hormone replacement product would often be more effective than an antihypertensive agent that obscures the cause. Incidentally, there are many additional benefits of this therapy, such as improved metabolic status and prevention of joint diseases, osteoporosis, and malignant diseases (such as colon cancer and vulvar cancer). Hypertension can also be caused by a lack of sleep due to working conditions or by slow but steady changes in personal lifestyle. Long-term work in night shifts is also worth mentioning, as this is common in both the health and the care sectors and primarily affects women. Often, these women are also burdened with family and household care. One cannot assume that, because the body can compensate for working night shifts for 10 years, it can also do it for 20 years. Treating this causally would potentially mean a drastic change of lifestyle or job, yet anything is better to unmask this condition than using an antihypertensive, perhaps with a fulminant outcome. If signs of atherosclerosis are already present, an immediate cardiovascular diagnosis is indicated, for example to exclude a relevant carotid stenosis as a cause, before pharmaceutical treatment is started. For hypertension therapy, the physician's first thought should not be to wonder which antihypertensive drug would be the right one, but rather how to determine the specific causes in this individual patient.

DOI: 10.3238/arztebl.2019.0070a

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Conflict of interest statement
The author declares that no conflict of interest exists.

Evidence-Based Blood Pressure Goals

The recommendation to further reduce blood pressure in patients with renal insufficiency or diabetes is not evidence-based: for renal insufficiency, there is no evidence of benefit for having target values <140/90 mm Hg (1); for diabetes mellitus, it can even be harmful (2). Lowering diastolic blood pressure <80–70 mm Hg for people over 65 is not only not evidence-based—this recommendation seems downright dangerous for older people. It remains completely incomprehensible why the recommendations of the German College of General Practitioners and Family Physicians' (DEGAM) S3 Guideline on Cardiovascular Prevention of 2017 (3), which is valid in Germany, was not mentioned in the article (4). In the Guideline, an unanimous consensus was reached for the following recommendations (as well as for others):

- The primary goal of antihypertensive treatment is to reduce the overall cardiovascular risk. In general, the target blood pressure should be ≤140 mm Hg systolic and ≤90 mm Hg diastolic.
- For persons over 80, the decision to start or stop therapy should be made on a case-by-case basis.

The primary selection of antihypertensives should be based on efficacy, tolerability, comorbidities, and cost.

DOI: 10.3238/arztebl.2019.0070b

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Conflict of interest statement
The author declares that no conflict of interest exists.

Off to a Bad Start With Fixed Combinations

The authors cite the new ESC guideline recommendations of directly starting a fixed combination of antihypertensive agents for persons with significantly high blood pressure (or those at an increased risk for it) (1, 2). However, there are no studies to date that compare cardiovascular events in monotherapy versus combination therapy (2). Instead, the rational given are the high rates (25%–65%) of poor adherence to therapies with multiple antihypertensive drugs; however, these rates were reported for patients with treatment resistance or in tertiary care (3, 4) and are therefore not transferable to primary care. From the point of view of primary care, controllability of the individual drugs in the phase of blood pressure adjustment makes sense and allows the adverse reactions specific for each drug to be more easily recognizable. Many fixed combinations are significantly more expensive than single drugs. This is particularly true for the combinations of ACE inhibitors and AT1 blockers with calcium antagonists shown in *Figure 5* in the article. When therapy was started in the hospital, diuretic combinations are often overdosed afterwards in the home environment because of the delayed-onset effect. Starting a fixed combination in the inpatient phase requires the primary care physician to carry out a time-consuming adjustment of medication after discharge.

DOI: 10.3238/arztebl.2019.0070c

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Conflict of interest statement
The author declares that no conflict of interest exists.

Small Target Group

The authors do not mention the Disease Management Programs (DMP) that are valid in Germany (DMP-Coronary Heart Disease [CHD; *Koronare Herzkrankheit, KHK*] or DMP-Diabetes), the National Health Care Guidelines (for diabetes or CHD), or the AWMF S3 Guideline on Cardiovascular Prevention of the German College of General Practitioners and Family Physicians (DEGAM) (1, 2). Instead, they cite mainly the guideline of the European Society of Cardiology (ESC) with high industrial dependence (3). Furthermore, if the intention is to refer to international recommendations for the wider medical profession, the ACP/AAFP Guidelines should have been mentioned (4), as these would inform the readers about which of the interventions are based on good data and strong recommendations, and which of the recommendations preferred by the authors represent actionism. In the inpatient area, disease prevalence and severity, as well as questions of liability and recourse, are quite different than in outpatient primary care or in the specialist area. For outpatient practices, many of the recommendations in the article are therefore neither evidence-based nor feasible. Since a principle of guidelines is that they should be compiled by a specific target group (and therefore can only be applied to it), it can be assumed that the ESC guideline—and subsequently also the article written by authors who work in hospitals—only applies for cardiologists working in hospitals. It remains unclear why a recommendation for such a small user group was not clearly indicated as such, but instead was even upgraded to a CME article.

DOI: 10.3238/arztebl.2019.0071a

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Genetic Factors Should Be Considered

Secondary hypertension is rare. Nonetheless, it should also be considered preemptively when caring for patients with incidentally discovered adrenal masses, which are initially clinically inapparent, for instance, subclinical hyperaldosteronism, subclinical Cushing's syndrome, or subclinical pheochromocytoma. Blood pressure is often still in the so-called normal range, which however is not necessarily normal for the individual patient (1). For example, normotensive pheochromocytomas occur in about one-third of patients with a mutation in the von Hippel-Lindau gene, as well as in other patients (2). One can measure not only free plasma metanephrines but also urinary fractionated metanephrines. In patients with Cushing's syndrome, it is often helpful to determine a salivary diurnal cortisol profile, especially for patients taking medications (such as contraceptives) that may lead to a false-positive (or false-negative) result in dexamethasone suppression tests (3). Knowledge of the CYP450 3A4 system is important (https://drug-interactions.medicine.iu.edu/Main-Table.aspx). Rare genetic disorders with mineralocorticoid excess are often discovered in childhood, but may also be diagnosed later, for example in connection with hypertension in a phenotypically adolescent girl with amenorrhea (17-alpha-hydroxylase deficiency; see also [3, 4]).

DOI: 10.3238/arztebl.2019.0071b

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Conflict of interest statement
The author declares that no conflict of interest exists.

Potential Drug Interactions Forgotten

The authors are to be thanked for the successful, very practice-oriented, and balanced evidence-based presentation (1). In the Pharmacotherapy section, they note that dihydropyridine-type calcium channel blockers can, in principle, be combined with all other first-line antihypertensive agents. This can be agreed upon unconditionally, although the development of peripheral edema is a frequent but dose-dependent side effect (2). After mentioning constipation as a potential side effect in elderly and immobile patients, the authors point out—although with too little differentiation, in our opinion—possible drug interactions with calcium channel blockers. To counter any possible confusion on the part of the readers, it should be emphasized that, from a clinical-pharmacological viewpoint, drug interactions for the dihydropyridine type of drugs due to inhibition of cytochrome P450 3A4 are almost irrelevant clinically but instead are only known for the verapamil/diltiazem type of calcium channel blockers. This type of drug in turn is not very significant for standard hypertension care. However, for the antihypertensives of the dihydropyridine-type listed in *Table 2*, it should be noted that amlodipine has a clinically relevant interaction with simvastatin, which plays a

role in the frequent multiple therapies used for treating comorbid dyslipidemia. Both drugs are metabolized in the intestine and liver, mainly by cytochrome P450 3A4/5. This leads to dose-dependent competition with this isoenzyme, with the result that amlodipine reduces the first pass metabolism of simvastatin (which is normally very pronounced), leading to an increased plasma concentration of statins (3). This in turn is associated with a higher risk of myopathy (4), which is why most specialist information sets a maximum simvastatin dose of 20 mg per day when amlodipine is taken concomitantly

DOI: 10.3238/arztebl.2019.0071c

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Conflict of interest statement
The author declares that no conflict of interest exists.

In Reply:

The pathophysiology of arterial hypertension is multifactorial. We could not consider all mechanisms (1). Unfortunately, the individual mechanisms that cause a rise in blood pressure usually cannot be identified. Our colleague Dr. Swalve-Bordeaux points out that blood pressure in postmenopausal women often increases and suggests that this increase in blood pressure should be counteracted with estrogen replacement. We consider this proposal to be extremely problematic, as recent meta-analyses of large clinical trials have shown that estrogen administration (with or without progesterone) in the context of primary prevention provides minor benefits in some areas, yet increases serious complications in others (2). For instance, receiving only estrogens increases the risk of stroke. In contrast, antihypertensive therapy has been clearly proven to reduce the risk of stroke. The comment that sleep deprivation is an underestimated risk factor for arterial hypertension is supported by epidemiological studies (3). We consider the decrease in mean sleep duration in many countries to be alarming. A form of secondary hypertension should be considered especially for patients with early onset hypertension, blood pressure that remains uncontrolled, or suspicious concomitant clinical symptoms and findings. Prof. Koch reminds us that these rarer diseases can have an atypical presentation. We should always subject clinical diagnoses—whether for hypertension or any other area of clinical medicine—to regular review. However, an untargeted search for cause in all patients with hypertension cannot be recommended.

We thank Dr. Regenthal for clarification of the adverse effects and drug interactions of calcium antagonists. The interaction between amlodipine and simvastatin is of importance because both drugs are prescribed very frequently. A combination of 80 mg simvastatin and 10 mg amlodipine per day has a potentially clinically relevant interaction. The maximum recommended dosage of simvastatin in concurrent use with amlodipine varies between 20 and 40 mg per day. If this dosage is insufficient, statins with a lower potential for interaction with amlodipine, such as atorvastatin, pravastatin, fluvastatin, or rosuvastatin, may be used.

Dr. Mehrländer questions the increasing emphasis on initial antihypertensive combination therapy using fixed combination preparations. In fact, there is no clear evidence that one or the other approach is preferable (4). As stated (1), we consider the initiation of combination therapy to be useful for patients with high blood pressure for whom a monotherapy is not expected to suffice for blood pressure control. For patients who are elderly or who present with concomitant diseases, having a greater control over the therapy by using free drug combinations may be beneficial.

Dr. Uebel and Dr. Egidi correctly stated that we did not take into account all the current guidelines. The S3 guideline on Risk Counseling on Cardiovascular Prevention in Family Medicine, in which Dr. Egidi was involved, provides a very meaningful framework for cardiovascular risk prevention. Not all clinical data included in the international hypertension guidelines have been included here. Most data on which the recommendations of current guidelines and our review are based have been generated in outpatient clinical trials. However, the patient population in clinical trials often represents a positive selection. The assertion that a guideline is only valid if it was created using the target group is unsubstantiated. The guidelines agree that lowering blood pressure can reduce cardiovascular risk, and especially the risk of stroke. However, lowering blood pressure too much also carries risks. Reviews and guidelines can only provide a framework for individual clinical decisions, especially when adjusting and implementing target values for blood pressure. Meaningful therapy decisions can only be made based on both clinical expertise and dialogue with the patient. Equally important is the good cooperation between primary care physicians, who care for the majority of patients with hypertension, and specialists, whose expertise is particularly required for difficult-to-adjust and complex cases.

DOI: 10.3238/arztebl.2019.0072

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Conflict of interest statement
Prof. Jordan has received scientific consultant honoraria from Bayer, Eternygen, Johnson & Johnson, Novartis, Novo-Nordisk, and Theravance and is co-founder of Eternygen GmbH.