Safety of Temporary Discontinuation of Antihypertensive Medication in Patients With Difficult-to-Control Hypertension

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Abstract—Successful control of blood pressure relies on identification of secondary causes and contributing factors of hypertension. As antihypertensive medication can interfere with diagnostic investigations, temporary discontinuation of medication is advised. However, there are concerns about the safety of temporary discontinuation of antihypertensive medication in patients with difficult-to-control hypertension. We assessed the occurrence of adverse cardiovascular and cerebrovascular events potentially attributable to temporary discontinuation of antihypertensive medication between February 2010 and March 2016 (n=604) in our Analysis of Complicated Hypertension screening program. A reference group (n=604) was extracted from the SMART study (Second Manifestations of Arterial Disease) cohort (comprising a similar cohort at our hospital in whom medication was not stopped) and individually matched for blood pressure, age, sex, and history of cardiovascular disease. Discontinuation of medication was well tolerated; 62% reported no complaints, 24% had mild discomfort that could be left untreated, and 14% experienced complaints that required prescription of antihypertensive escape medication. Three major adverse events were observed in the Analysis of Complicated Hypertension group between discontinuation of medication and 30 days after restart of medication (event rate=31.2 events per 1000 patient-year). In the reference cohort, 5 cardiovascular events were observed during a similar follow-up period (event rate=51.2 events per 1000 patient-year). In conclusion, discontinuation of antihypertensive medication for the diagnostic evaluation of hypertension does not increase the acute risk of cardiovascular events when performed in a well-controlled setting in specialized hospitals with appropriate protocols for monitoring safety. **(*Hypertension*. 2017;69:927-932. DOI: 10.1161/HYPERTENSIONAHA.116.08793.)**

Key Words: antihypertensive agents ■ blood pressure ■ cardiovascular diseases ■ hypertension ■ stroke

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The increased risk of stroke, coronary heart disease, and vascular mortality related to hypertension can be significantly reduced by long-term control of blood pressure (BP).[1,2] Yet, control rates of hypertension are still disappointingly low.[3] Patients with difficult-to-control hypertension form a special subgroup of patients with uncontrolled BP, as secondary causes are more prevalent in this population.[4] These patients may particularly benefit from an extensive diagnostic work-up for identification of potential secondary causes, nonadherence, and contributing factors.

Concurrent use of antihypertensive drugs (AHD) impedes the establishment of secondary causes for hypertension because they can interfere with the (biochemical) diagnostic tests. Particularly the renin–angiotensin–aldosterone system axis is influenced by various AHDs, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists, and β-blockers.[5–8] For example, the prevalence of primary hyperaldosteronism ranges from 6% in an unselected hypertensive population to 11% in resistant hypertension, increasing up to 18% when interfering medication is stopped before the investigations.[9–12] It is therefore advised to temporarily discontinue antihypertensive medication before the diagnostic investigations.[13] Yet, the scientific evidence that temporary discontinuation of AHD is safe in this high-risk population is still lacking. In the majority of patients, discontinuation of AHD will result in an asymptomatic return of BP to pretreatment levels only. A small minority may experience a syndrome known as withdrawal syndrome or discontinuation syndrome. This syndrome is characterized by rapid return or overshoot of BP with signs and symptoms of sympathetic overactivity and is associated with an increased acute risk of cardiovascular and cerebrovascular

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events.[14] The extent of this risk during temporary discontinuation of AHD in a high-risk population has not yet been well researched. Therefore, we aimed to evaluate the safety of temporary discontinuation of antihypertensive medication as part of a highly standardized diagnostic protocol in patients with difficult-to-control hypertension.

Methods

This study analyzed the electronic record data of patients undergoing the Analysis of Complicated Hypertension (ACH) at the University Medical Center Utrecht in Utrecht, The Netherlands. A reference group was extracted from the SMART cohort (Second Manifestations of Arterial Disease).[15,16] All data were deidentified for research purposes, according to the Dutch Medical Research involving Human Subjects Act and the Dutch Personal Data Protection Act. The study was approved by the Medical Ethics Committee of the University Medical Center Utrecht and executed in accordance with the Good Clinical Practice guidelines. The need for written informed consent was waived by the Medical Ethics Committee.

Patient Population

The patient population consisted of all patients who were referred for difficult-to-control hypertension and who entered the ACH program between February 2010 and March 2016. The ACH is a highly standardized diagnostic program designed to identify secondary causes of hypertension, identify contributing factors of hypertension, and assess overall cardiovascular risk profile in patients with difficult-to-control hypertension (ie, persistent hypertension despite optimal treatment according to the current guidelines and the presence of end-organ damage or vascular complications). A schematic overview is provided in Figure 1. Patients who were not taking any AHDs at the time of referral and patients in whom all medication was continued during the screening program were excluded from analysis.

Discontinuation of Antihypertensive Medication

At the outpatient clinic, a hypertension specialist assessed whether it was deemed safe to discontinue medication. Cardiovascular events (ie, myocardial infarction, stroke, or transient ischemic attack [TIA]) within 6 months before the ACH program were an absolute contraindication for discontinuation of AHD. Relative contraindications included other cardiovascular comorbidities (eg, stable coronary artery disease) or severe hypertension (defined as a treated BP >180/110 mm Hg or history of hypertensive urgency requiring hospital admission). Antihypertensive medication was stopped in a protocolled staged fashion (Figure 1). B-blockers and central-acting AHD were tapered down in 2 weeks to avoid medication withdrawal syndrome. During the screening period, protocolled dosages of diltiazem, doxazosin, or verapamil were available as escape medication, as they do not interfere with the biochemical evaluation of the aldosterone–renin ratio. Escape medication could be prescribed at the start of the screening (preventive, eg, in case of a relative contraindication) or at any time during the screening if considered necessary by the treating hypertension specialist or (if unavailable) the specialist on call. Indications to start escape medication during the screening included a dangerous increase in BP occurred (generally >180/110 mm Hg) or if the patient experienced severe anxiety or complaints.

Safety Monitoring During Medication Withdrawal

All patients received a personalized withdrawal schedule and were instructed to contact the hospital 24/7 if BP increased >180 mm Hg systolic or 110 mm Hg diastolic on home BP monitoring, if alarm symptoms occurred, or if the patient felt insecure or had any questions. BP was monitored during the medication withdrawal by home BP measurements that were uploaded to a secure internet site and visible to the appropriate staff at the hospital. One week after the last AHD was stopped, patients received a scripted telephone call by the nurse practitioner to identify possible side effects and potential complications. During the telephone call, the home BP measurement levels were evaluated and patients were specifically asked for complaints of headache, dizziness, visual complaints, and chest pain.

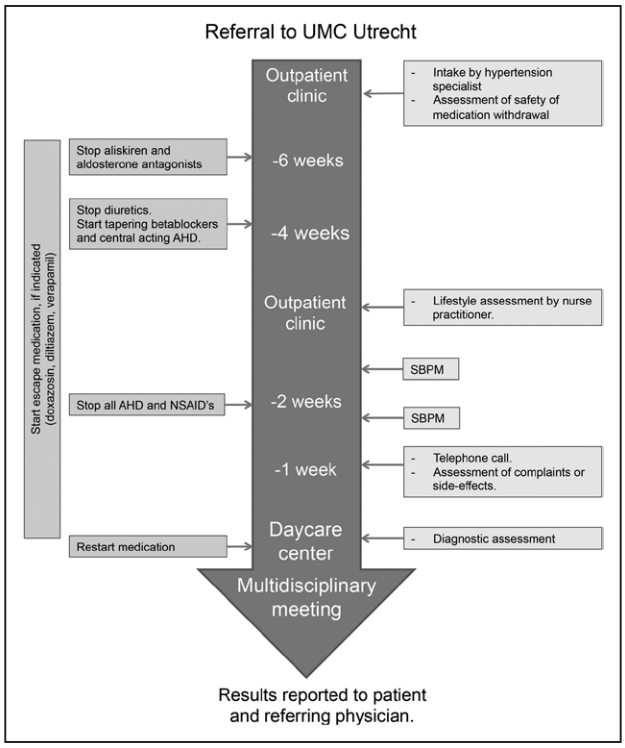

Figure 1. Overview of the diagnostic work-up for difficult-to-control hypertension. Overview of the diagnostic work-up with temporary medication withdrawal for patients with difficult-to-control hypertension. The blue arrow represents the timeline of the diagnostic program. The schedule for the withdrawal of antihypertensive medication is depicted on the left hand side of the arrow, the appointments and assessments during the program are depicted on the right hand side. AHD indicates antihypertensive drugs; NSAID, non-steroid anti-inflammatory drugs; SBPM, self-blood pressure monitoring; and UMC, university medical center.

Reference Group

We used the SMART cohort to construct a reference group to compare the occurrence of adverse events with a similar population who did not discontinue medication. The SMART study is an ongoing, single-center, prospective cohort study of patients newly referred to our hospital with clinically manifest atherosclerotic vessel disease or marked risk factors for atherosclerosis.[15,17] Patients who were included in both the ACH and SMART cohorts were filtered from the SMART cohort before each ACH patient was matched 1 to 1 for SBP and 10-year risk of cardiovascular events to a SMART subject, with maximally tolerated differences of 15 mm Hg or 3%, respectively.

End Points

The primary end point was defined as the occurrence of major adverse cardio- and cerebrovascular events between the start of medication withdrawal and 30 days after restart of medication. Major adverse cardio- and cerebrovascular events was defined as (1) cardiovascular death, (2) nonfatal acute coronary syndrome, (3) acute heart failure, or (4) nonfatal stroke (including subarachnoid hemorrhage and TIA). Because the reference group had no medication withdrawn, a surrogate time window of 59 days (the mean follow-up in the ACH group) after inclusion was used. The end points defined in SMART were similar to the end points defined for the ACH, but did not include TIA.

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As secondary outcome for the ACH group, we assessed the occurrence of BP-related complaints and visits to the emergency department during medication withdrawal.

Data Analysis

Results are presented as mean±SD, median (interquartile range), or as an absolute number with percentages unless otherwise specified. Dosages of AHD were converted into defined daily doses using conversion factors provided by the World Health Organization Collaborating Centre for Drug Statistics Methodology.[18] The 10-year risk for cardiovascular disease was calculated for each individual using the Framingham score[19] for individuals without previous cardiovascular disease and the SMART risk score[16] for patients with a history of cardiovascular events. Between-group differences for continuous variables were analyzed using the independent samples *t* test or Mann–Whitney *U* test, as appropriate. For categorical variables, the χ^2 test was used. Life tables were used to analyze event-free survival and expressed as event rate per 1000 patient-year. Results were considered statistically significant if the 95% confidence interval (CI) did not include 0 or if the 2-tailed *P* value did not exceed 0.05. All analyses were performed with SPSS statistical software version 22 (IBM SPSS Data Collection, Chicago, IL).

Results

Between 2010 and 2016, 692 patients entered the ACH program. Eighty-eight patients were excluded from analysis; of those, 72 patients were not taking any AHD at the time of referral, 2 patients continued all medication during the ACH, for 11 patients the program was put on hold before medication withdrawal, and 3 patients decided against the screening program. The remaining 604 patients were included in the current analysis and could be individually matched to a reference subject. The patient characteristics of both groups are depicted in Table 1. In the ACH group, 457 patients (76%) completely discontinued all medication throughout the screening program, whereas 147 patients (24%) had escape medication prescribed. Escape medication was prescribed as an intervention for (complaints of) high BP in 82 patients (see also below), as prevention for relative contraindications in 64 patients, and 1 patient accidentally continued an AHD during the screening.

Major Adverse Cardio- and Cerebrovascular Events

In the ACH group, 3 major adverse events occurred during a mean follow-up of 59 days (ranging from 42 to 72 days), corresponding to an event rate of 31.2 events per 1000 patient-year (95% CI, 6.4–91.2). In short, a 68-year-old woman with a history of cardiac complaints experienced a mild non–ST-segment–elevation myocardial infarction 3 days after complete withdrawal of medication. She was treated with staged percutaneous coronary intervention for 3-vessel disease. A 66-year-old man with a history of atrial fibrillation and a non–ST-segment–elevation myocardial infarction was diagnosed with TIAs in the posterior circulation 2 days after restart of medication. Finally, a 63-year-old man with a history of peripheral and coronary arterial disease was diagnosed with a sick sinus syndrome and transient unstable angina pectoris during atrial fibrillation 28 days after restart of medication, for which he received a scheduled percutaneous coronary intervention. All 3 patients had above-average baseline office BP (respectively, 180/96 mm Hg, 198/108 mm Hg, and 190/100 mm Hg, versus 172/98 mm Hg). In the reference group also 3 major adverse events occurred during follow-up (59 days for all patients), corresponding to an event rate of 30.7 events per 1000 patient-year (95% CI, 7.8–84.2). A 70-year-old man experienced an ischemic stroke, a 53-year-old woman experienced a cardiac event requiring coronary bypass surgery, and a 51-year-old man required percutaneous coronary intervention for a cardiac event.

Tolerability of Medication Withdrawal in ACH

Figure 2 depicts the occurrence of the most common complaints and the need for treatment during the ACH program. The majority of patients completed the ACH program and medication withdrawal without any side effects (n=373; 62%) or with mild discomfort (eg, slight headache or tiredness) that did not require escape medication (n=149; 24%). Eighty-two patients (14%) reported complaints that led to the prescription of escape medication.

Twenty-six ACH patients (4%) visited the emergency department during or after medication withdrawal. In 23 cases of them, no adverse event could be demonstrated and the ACH could continue without any further obstacles. Two patients experienced complaints that were attributed to the discontinuation of medication for the ACH program. One patient was admitted for severe hypertension (199/133 mm Hg) while not taking the prescribed escape medication (diltiazem). He was treated with escape medication (diltiazem plus doxazosin) and discharged the following day. Another patient developed atrial fibrillation during an episode of fever because of laryngitis while he was tapering his β-blocker, for which the ACH was postponed. Finally, 1 patient experienced an adverse event not directly related to the withdrawal of medication; she experienced dizziness possibly related to a hypokalemia of 2.7 mmol/L (reference value, 3.8–5.0) and dislocated her shoulder in a fall. The ACH analysis later demonstrated primary hyperaldosteronism based on an adrenal adenoma causing the hypokalemia.

Discussion

We reported our 6-year experience with temporary discontinuation of AHDs in the context of the diagnostic work-up of patients with difficult-to-control hypertension. When performed in a highly structured program with careful patient selection and protocol for monitoring patient safety, short-term withdrawal of antihypertensive medication does not seem to increase the acute risk of major vascular events. In addition, temporary discontinuation of medication was well tolerated by the vast majority of patients, as 86% of patients experienced no complaints or only experienced mild discomfort that required no intervention. Our findings may have important clinical implications for the diagnostic evaluation of difficult-to-control hypertension. As mentioned in the first paragraph, temporary withdrawal of antihypertensive medication can improve the accuracy of diagnostic tests for secondary hypertension. However, temporary discontinuation of antihypertensive medication is not without controversy in this population with difficult-to-control hypertension and subsequent high cardiovascular risk. Physicians may be reluctant to interrupt treatment in this population, fearing major cardiovascular complications with potential irreversible damage.

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Table 1. Patient Characteristics

Patient Characteristic	Study Cohort (n=604)	Reference Cohort (n=604)
Age, y	54±13	50±15
Sex, male	292 (48%)	290 (48%)
Office SBP (treated), mm Hg	172±26	165±27
Office DBP (treated), mm Hg	98±14	94±16
Office SBP (untreated), mm Hg	167±23	N/A
Office DBP (untreated), mm Hg	98±14	N/A
24-h SBP (untreated), mm Hg	153±19	N/A
24-h DBP (untreated), mm Hg	93±12	N/A
CVD		
Cardiac	68 (11%)	30 (5%)
Cerebral	59 (10%)	30 (5%)
AAA	3 (<1%)	7 (1%)
PAD	17 (3%)	19 (3%)
BMI, kg/m^2	28±4.9	27±5.3
Total cholesterol, mmol/L	5.3±1.1	5.6±1.6
HDL-C, mmol/L	1.3±0.4	1.3±0.4
LDL-C, mmol/L	3.2±1.0	3.5±1.3
Triglycerides	1.6±1.1	2.1±4.1
Diabetes mellitus	71 (12%)	168 (27.8%)
eGFR, mL/min per 1.73 m2	82±25	82±22
Smoking		
Current	70 (12%)	175 (29%)
Stopped	263 (44%)	161 (28%)
Never	261 (44%)	268 (44%)
Pack-years	17±17	11±17
10-y CV risk, %	9.3±8.3	9.8±10.9

Patient characteristics of the study population (medication withdrawal) and reference cohort. Reference cohort was matched for SBP, age, sex, and history of CVD. eGFR was calculated using the chronic kidney disease–epidemiology collaboration (CKD-EPI) formula. Untreated BP represents office BP after discontinuation of AHD. AAA indicates abdominal aorta aneurysm; BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein- cholesterol; PAD, peripheral artery disease; and SBP, systolic blood pressure.

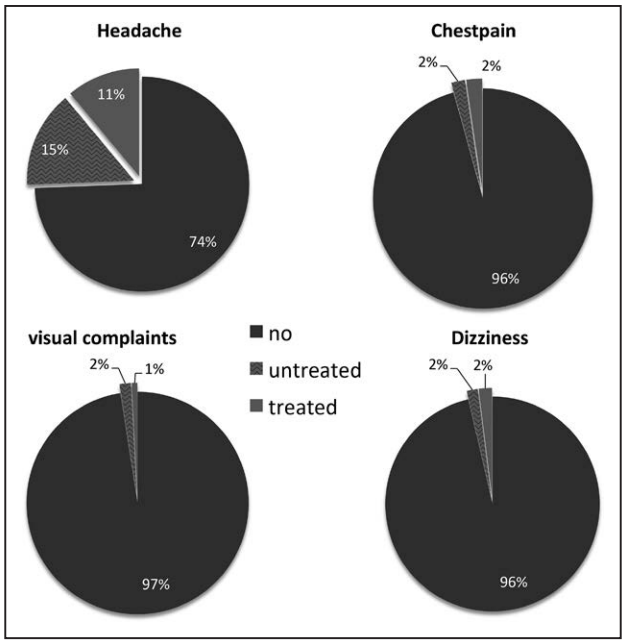

Figure 2. Complaints during medication withdrawal and need for treatment.

Our results indicate that temporary withdrawal of medication does not increase the acute risk of major adverse cardio- and cerebrovascular events when performed in a well-controlled setting. We demonstrated an equal number of events in the study group, compared with the reference group with a similar cardiovascular risk that did not discontinue medication. The event rate in our cohort was lower than in most reported placebo arms of large randomized pharmacological hypertension trials, and similar or slightly higher than in their treatment study arms (Table 2). However, there are 2 major differences between these trials and our study that need to be taken into account. First, we included TIAs and unstable angina pectoris in our definition of major adverse cardio- and cerebrovascular events to have a low threshold for adverse events. These events are generally not included in the end point definition of the abovementioned hypertension trials, resulting in a relative overestimation of events in our study. Second, in our study, medication was discontinued for a limited amount of time only, resulting in wide CIs compared with hypertension trials where patients are assigned to placebo for several months to years.

Studies investigating the short-term effect of antihypertensive medication compared with placebo are scarce. We know of 2 meta-analyses that investigated short-term placebo-controlled trials, one of which assessed (mostly unpublished) data submitted to the Food and Drug Administration. Both demonstrated no differences in event rates between intervention and placebo.[26,27] When defining adverse events as a composite end point similar to ours (death, nonfatal stroke, TIA, nonfatal congestive heart failure, nonfatal myocardial infarction, and angina pectoris), the event rate in the meta-analysis of DeFelice et al[27] was 29.2 per 1000 patient-year for placebo arms compared with 31.2 per 1000 patient-year in our study. These findings further support our conclusion that short-term interruption of treatment does not seem to affect the acute risk of major adverse events and irreversible harm.

Our results may not only benefit the routine clinical care of hypertension but may also be of specific interest to device-based intervention trials. The research involving renal denervation treatment for hypertension has uncovered some important shortcomings and confounders in various trials, most importantly the influence of AHD on BP outcomes. To overcome these issues, several trials have been announced to involve washout of AHD and medication-free end point measurement (such as the Spyral HTN OFF-MED [Symplicity Spyral Multi-Electrode Renal Denervation System in Patients With Uncontrolled Hypertension in the Absence of Antihypertensive Medication],[28] the Vessix REDUCE HTN: REINFORCE [Renal Denervation Using the Vessix Renal

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Table 2. Event Rates in Different Arms of Hypertension Trials

Study	Age, y	Baseline BP	ΔBP	Events / 1000 PY	95% CI	Intervention
SHEP[20] (1991)	72±7	170/77	−27/−9	18.7	16.2–21.4	Chloortalidon±atenolol
	72±7	170/77	−15/−5	27.1	24.1–30.4	Placebo
SYST-EUR[21] (1997)	70±7	174/86	−23/−7	23.3	19.3–26.9	Nitrendipine
		174/91	−13/−2	33.9	28.1–37.5	Placebo
LIFE[22] (2002)	70±7	174/98	−30/−17	23.8	21.1–25.1	Losartan
		175/98	−29/−17	27.9	24.6–29.0	Atenolol
VALUE[23] (2004)	67±8	154/87	−15/−8	25.5	23.5–27.0	Valsartan
		155/88	−17/−10	24.7	23.1–26.5	Amlodipine
FEVER[24] (2005)	62±7	154/91	−17/−8	26.4	23.9–29.0	Felodipine
		154/91	−11/−6	37.6	33.8–39.7	Placebo
HYVET[25] (2008)	84±3	173/91	−15/−19	33.7	33.5–46.7	Indapamide±perindopril
		173/91	−7/−11	50.6	48.6–64.4	Placebo
Present study	54±13	172/98	−6/0	31.2	6.4–91.2	Cessation of AHD

Table depicts main study characteristics for the present study and recent large hypertension trials that provided event rates for major adverse cardiovascular events. If not provided in the original article, event rates and 95% CIs were calculated using an online epidemiological calculator and may therefore differ slightly from the original when using the actual observed data. Age is measured in years, blood pressure is measured in mm Hg. AHD indicates antihypertensive drugs; BP, blood pressure; CI, confidence interval; FEVER, The Felodipine Event Reduction; HYVET, Hypertension in the Very Elderly Trial; LIFE, Losartan Intervention for Endpoint Reduction; PY, patient-year; SHEP, Systolic Hypertension in the Elderly Program; SYST-EUR, The Systolic Hypertension in Europe; and VALUE, Valsartan Antihypertension Long-Term Use Evaluation.

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Denervation System for the Treatment of Hypertension; NCT02392351], and the RADIANCE-HTN [Study of the ReCor Medical Paradise System in Clinical Hypertension; NCT02649426] trials). Our results may guide researchers in the design of their protocol and diminish ethical objections when temporary discontinuation is required for study entry or end point measurement. Yet, our results may not apply to prolonged AHD cessation throughout several months of follow-up or to patients with controlled hypertension if BP increases in response to AHD discontinuation.

When interpreting our results, one should be aware of the limitations to our reference group. The ACH program has been a common clinical practice in our hospital since 2010. All patients referred for the analysis of difficult-to-control hypertension are subjected to the same program, including the withdrawal of antihypertensive medication. Therefore, no control group could be included that underwent the ACH program with continuation of medication. We tried to overcome this by creating a reference group from the SMART study, in which population closely resembles the ACH population. Furthermore, patients were individually matched for BP, age, sex, and cardiovascular history to optimize comparability of both populations. Although this approach is suboptimal compared with a true control group (preferably with a randomized design), the reference group provided the best available opportunity to place our results into perspective.

Interestingly, we observed a small decrease in average systolic BP and a lack of change in diastolic BP after discontinuation of antihypertensive medication, whereas an increase in these pressures might have been expected.

Perspectives

Our results indicate that the temporary (up to 6 weeks) discontinuation of antihypertensive medication for the diagnostic evaluation of hypertension does not increase the acute risk of cardiovascular events, provided it is performed in a well-controlled setting in specialized hospitals with appropriate protocols for monitoring safety. Our institutionally devised protocol with extensive safety monitoring does not reflect the conditions of routine medical care, and similar protocols should only be applied in dedicated healthcare facilities with expert knowledge on the management of patients with difficult-to-control hypertension. Special attention should be given to careful patient selection, as patients who carry increased risk (eg, those with high baseline BP levels and a history of cardiovascular disease) may require continuation of medication or preventive escape medication. When performed with proper regard for patient selection and safety, diagnostic screening programs including a strategy for safe discontinuation of medication will likely increase the diagnosis of secondary causes of hypertension and reduce bias in hypertension research.

Disclosures

None.

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Novelty and Significance

What Is New?

- We demonstrated that temporary discontinuation of antihypertensive medication for diagnostic purposes in a well-controlled setting does not increase the risk of adverse cardio- and cerebrovascular disease in a population of patients with difficult-to-control hypertension, compared with patients at the same hospital in whom medication was not discontinued.

What Is Relevant?

- Concomitant use of antihypertensive medication interferes with biochemical tests and changes in antihypertensive medication impede reliable blood pressure measurements in hypertension research. Temporary discontinuation of antihypertensive medication may increase the accuracy of diagnostic tests for secondary hypertension and may increase the reliability of blood pressure end points in trials investigating device-based treatment for hypertension.

Summary

Discontinuation of antihypertensive medication for the diagnostic evaluation of hypertension does not increase the acute risk of cardiovascular events, when performed in a well-controlled setting in specialized hospitals with appropriate protocols for monitoring safety.

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