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

Martine M.A. Beeftink, Nicolette G.C. van der Sande, Michiel L. Bots, Pieter A. Doevendans, Peter J. Blankesteijn, Frank L.J. Visseren, Michiel Voskuil, Wilko Spiering

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

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...
events. 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). 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 diuretics, calcium-channel blockers, 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.

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.
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. The 10-year risk for cardiovascular disease was calculated for each individual using the Framingham score for individuals without previous cardiovascular disease and the SMART risk score 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 χ² 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 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 mmHg) 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.
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 TIs 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 al27 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 measurements (such as the Spyral HTN OFF-MED [Simplicity Spyral Multi-Electrode Renal Denervation System in Patients With Uncontrolled Hypertension in the Absence of Antihypertensive Medication],26 the Vessix REDUCE HTN: REINFORCE [Renal Denervation Using the Vessix Renal

### Table 1. Patient Characteristics

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

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.
Therefore, no control group could be included that under-
including the withdrawal of antihypertensive medication.
2. Patients referred for the analysis of difficult-to-
has been a common clinical practice in our hospital since
the limitations to our reference group. The ACH program
up or to patients with controlled hypertension if BP increases
when temporary discontinuation is required for study entry or
the design of their protocol and diminish ethical objections
NCT02649426 trials). Our results may guide researchers in
ReCor Medical Paradise System in Clinical Hypertension;
NCT02392351, and the RADIANCE-HTN [Study of the
Denervation System for the Treatment of Hypertension; NCT02392351], and the RADIANCE-HTN [Study of the
MH, Weiss NS. Health outcomes associated with various antihypertensive
treatment of 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 pro-
longed AHD cessation throughout several months of follow-
up or to patients with controlled hypertension if BP increases
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,
only 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 sys-
tolic BP and a lack of change in diastolic BP after discontinu-
ation of antihypertensive medication, whereas an increase in
these pressures might have been expected.

Table 2. Event Rates in Different Arms of Hypertension Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Age, y</th>
<th>Baseline BP</th>
<th>ΔBP</th>
<th>Events / 1000 PY</th>
<th>95% CI</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHEP²¹ (1991)</td>
<td>72±7</td>
<td>170/77</td>
<td>−27/−9</td>
<td>18.7</td>
<td>16.2–21.4</td>
<td>Chloortalidon±atenolol</td>
</tr>
<tr>
<td>SYST-EUR²² (1997)</td>
<td>70±7</td>
<td>174/86</td>
<td>−23/−7</td>
<td>23.3</td>
<td>19.3–26.9</td>
<td>Nitrendipine</td>
</tr>
<tr>
<td>LIFÉ²² (2002)</td>
<td>70±7</td>
<td>174/96</td>
<td>−30/−17</td>
<td>23.8</td>
<td>21.1–25.1</td>
<td>Losartan</td>
</tr>
<tr>
<td>VALUE²³ (2004)</td>
<td>67±8</td>
<td>154/87</td>
<td>−15/−8</td>
<td>25.5</td>
<td>23.5–27.0</td>
<td>Valsartan</td>
</tr>
<tr>
<td>FEVER²⁴ (2005)</td>
<td>62±7</td>
<td>154/91</td>
<td>−17/−8</td>
<td>26.4</td>
<td>23.9–29.0</td>
<td>Felodipine</td>
</tr>
<tr>
<td>HYVET²⁵ (2008)</td>
<td>84±3</td>
<td>173/91</td>
<td>−15/−19</td>
<td>33.7</td>
<td>33.5–46.7</td>
<td>Indapamide±perindopril</td>
</tr>
<tr>
<td>Present study</td>
<td>54±13</td>
<td>172/98</td>
<td>−6/0</td>
<td>31.2</td>
<td>6.4–91.2</td>
<td>Cessation of AHD</td>
</tr>
</tbody>
</table>

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 mmHg. 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.

Perspectives

Our results indicate that the temporary (up to 6 weeks) dis-
continuation 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-con-
trolled setting in specialized hospitals with appropriate proto-
cols for monitoring safety. Our institutionally devised protocol
with extensive safety monitoring does not reflect the condi-
tions 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 cardio-
vascular 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 med-
ication will likely increase the diagnosis of secondary causes
of hypertension and reduce bias in hypertension research.

Disclosures

None.

References


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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