A Systematic Review of Predictors of Maintenance of Normotension After Withdrawal of Antihypertensive Drugs

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Background: The identification and treatment of hypertension in the general community has contributed to the reduction in strokes and coronary heart disease observed during the past 30 years. However, concerns have arisen that some patients may be receiving unnecessary antihypertensive drug therapy leading to wasted resources and the potential for adverse drug effects. Once therapy has been started, treating physicians have difficulty in selecting patients for withdrawal and have concerns regarding patient safety and their own legal liability.

Procedures: This study reviews and consolidates information from published studies to identify known predictors of the successful maintenance of normotension after antihypertensive drug withdrawal. The predictors were identified by determining the proportion of subjects with various baseline characteristics who remained normotensive while off medication for at least 12 months. From these data we have developed a clinical algorithm to help identify patients in whom antihypertensive drug withdrawal might be considered. This may assist primary care physicians in achieving successful withdrawal of antihypertensive therapy among selected hypertensive patients.

Results: The most consistent predictors identified were blood pressure (BP) (lower pretreatment, on treatment, and after withdrawal), nature of pharmacotherapy (fewer agents and lower dose), and preparedness to accept dietary intervention (weight and sodium reduction).

Conclusions: On the basis of this information, a trial of withdrawal of antihypertensive medication might be recommended for patients who have mildly elevated, uncomplicated BP that is well controlled on a single agent, and who are motivated and likely to accept lifestyle changes. Am J Hypertens 2001;14:98–105 © 2001 American Journal of Hypertension, Ltd.

Key Words: Withdrawal, antihypertensive drugs, predictors.

Approximately 10% of adults in Western countries are receiving long-term treatment with antihypertensive drugs. A proportion of these may be receiving treatment inappropriately, either because pharmacologic therapy was commenced without appropriate justification or because their hypertension has resolved with lifestyle change. Once treatment is started physicians are often reluctant to withdraw therapy because of the difficulty in distinguishing between those patients who need and those who do not need continued treatment.

Unnecessary drug treatment is costly to society and to individuals, and places subjects at risk of the adverse effects of drug treatment. However, drug withdrawal may also be a concern because of issues such as drug withdrawal effects and possible legal liability if cardiovascular events occur during or shortly after ceasing therapy.

In the present study we have systematically reviewed published studies on withdrawal of antihypertensive drugs to identify consistent predictors of successful cessation of therapy through an analysis of subject baseline characteristics and study criteria. The information was presented as an algorithm that might be of value to primary care physicians.

Methods

Articles examining withdrawal of antihypertensive drug therapy were identified from MEDLINE using various topic-related key words. Additional articles were identified from the bibliographies of these publications. Using this approach we believe that we have identified all English-
language publications examining the withdrawal of antihypertensive therapy published since the 1950s.

Each article was analyzed and key data concerning study design, definitions of hypertension and normotension, and baseline predictors were extracted. The criteria used for normotension varied among the individual studies. Therefore, successful withdrawal was defined as the maintenance of blood pressure (BP) levels below those where recommencement of drug treatment was advised 12 months after cessation of therapy. Studies with follow-up periods less than 12 months and those where the BP levels requiring recommencement of therapy were not specified were therefore excluded. Studies with very long follow-up periods were also excluded if it was not possible to estimate a 12-month success rate from the data provided by the investigators.

The monthly hazard (risk) of returning to hypertension was produced by computing the risk within each reported time interval and averaging over the interval time span. Summary relative risks describing the effects of gender, body weight reduction after withdrawal of antihypertensive drugs, and sodium reduction after withdrawal of an-
hypertensive drugs, on the likelihood of requiring recommencement of therapy were determined using the DerSimonian and Laird random effects model, together with tests for heterogeneity of effects across the studies.2 Because there was little heterogeneity, the summary relative risks reduce to those obtained from a fixed effect model.

Results
Forty-one studies were identified, with majority of which described observational studies or patients withdrawn from drug therapy during the run in phase of a clinical trial.3–45 Seven studies were excluded because of a follow-up period of less than 12 months,14,17,20,32–34,37 nine because of the absence of any estimate of success at 12 months,4,9,10,13,15,28,35,40,43 five because of the absence of criteria related to the recommencement of therapy,5,11,18,20,30 and eight because baseline characteristics provided could not be linked to an estimate of success at 12 months.12,14,16,21,23,31,41,45 The remaining twelve studies were considered to represent the pivotal studies and are summarized in Tables 1 and 2.

Table 3 show that the most consistent predictors identified among these studies were BP (lower pretreatment, on treatment, and after withdrawal), pharmacotherapy (fewer agents and lower dose), and dietary intervention (weight and sodium reduction).

Fig. 1 shows the risk of patients returning to hypertension at varying times after drug withdrawal among groups not receiving lifestyle intervention. It shows that the risk of return to hypertension is greatest in the first 6 months. However, the risk continues after this time.

Table 2. Pivotal study recommence therapy criteria and success rates for maintenance of normotension post withdrawal of antihypertensive drugs where predictors of success were investigated

<table>
<thead>
<tr>
<th>Study</th>
<th>Recommence Therapy BP Level (mm Hg)</th>
<th>% (n) Normotensive at 12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alderman et al3</td>
<td>1 visit ≥110, 2 visits ≥95 (&lt;65)</td>
<td>28% (44)</td>
</tr>
<tr>
<td>DISH6–8</td>
<td>1 visit ≥105, 2 visits ≥100, 3 visits ≥95</td>
<td>Placebo 35%</td>
</tr>
<tr>
<td>Grimm et al19</td>
<td>1 visit ≥115, 2 visits ≥95, 3 visits ≥90</td>
<td>56% (160)</td>
</tr>
<tr>
<td>Levinson et al22</td>
<td>1 visit ≥114, 2 visits ≥99, 3 visits ≥94</td>
<td>54% (79) Placebo</td>
</tr>
<tr>
<td>Medical Research Council24</td>
<td>&gt;90</td>
<td>41% (12)</td>
</tr>
<tr>
<td>Mitchell et al25</td>
<td>≥90</td>
<td>44% (5)</td>
</tr>
<tr>
<td>Morgan et al26</td>
<td>≥160/95*</td>
<td>47% (16)</td>
</tr>
<tr>
<td>Myers et al27</td>
<td>≥160/95*</td>
<td>44% (16)</td>
</tr>
<tr>
<td>Stamler et al36</td>
<td>≥160/95*</td>
<td>44% (16)</td>
</tr>
<tr>
<td>Takata et al38</td>
<td>≥160/95*</td>
<td>44% (16)</td>
</tr>
<tr>
<td>Thurm and Smith39</td>
<td>≥90</td>
<td>23% (16)</td>
</tr>
<tr>
<td>TONE42,44</td>
<td>1 visit ≥110, 2 visits ≥100, 3 visits ≥90</td>
<td>34% (NA)</td>
</tr>
</tbody>
</table>

BP = blood pressure; M = male; F = female; ACEI = angiotensin converting enzyme inhibitor; other abbreviations as in Table 1. * Represents ambulatory blood pressure measurement.
Discussion

In the pivotal studies reviewed the most consistent predictors of successful antihypertensive drug withdrawal were relatively low levels of BP, both before treatment was started and during therapy with a single drug. Adoption of lifestyle changes, such as reduced body weight and reduced sodium intake, after withdrawal were also useful predictors.

In a meta-analysis, reduced body weight and sodium restriction were also confirmed to be statistically significant predictors. These findings imply that a trial of drug withdrawal is most likely to be successful in patients with one or more of these characteristics, especially if the lifestyle changes are adopted.

These conclusions are based on a review of information from 12 studies shown in Tables 1 and 2. Most of these studies involved withdrawal of previous drug therapy as a prelude to participation in a clinical trial. The cohorts were then observed and the characteristics of those in whom hypertension recurred were compared with those in whom it remained low.

There are several limitations of the data from which the predictors are observed. The participants involved were not necessarily representative of hypertensive patients in general and the predictors examined varied from study to study and were not defined in a consistent fashion.

All studies, however, had at least 12 months of follow-up. In the absence of lifestyle interventions, success rates averaged approximately 42% over all studies with follow-up periods of this duration. With a single exception, the studies with follow-up periods between 2 and 5 years show similar rates of maintenance of normotension to
those where the follow-up period was limited to 12 months.\textsuperscript{3,12,13,16,24,36,42,44} The available information suggests that the rate of recurrence slows after 6 months (Fig. 1).

Many studies have noted that several weeks or months commonly elapse between the cessation of drug treatment and the return of BP to higher levels. This is believed to result from a reduction in hypertrophy in smaller arteries during treatment that reverses the elevated peripheral resistance.\textsuperscript{20} A considerable period may elapse before such hypertrophy redevelops. This illustrates the need to institute long-term monitoring of the BP of patients withdrawn from antihypertensive therapy with the aim of detecting a return of hypertension. As seen in Fig. 1 such monitoring needs to be most diligent in the first 6 months after withdrawal.

![Graph showing the hazard of returning to hypertension over time after withdrawal of antihypertensive drugs.](https://example.com/graph1.png)

**FIG. 1.** A multiple linear plot for studies with data of the “natural history” (ie, without a lifestyle intervention or placebo) of withdrawal of antihypertensive drugs and subsequent risk of return to hypertension over 12 months (n = 9).\textsuperscript{7,12,16,21,22,25,36,38,42} The monthly hazard of returning to hypertension was produced by computing the risk within each reported time interval and averaging over the interval time span. WAD = withdrawal of antihypertensive drugs.

Table 4. A meta-analyses of baseline characteristics as predictors of subjects who had antihypertensive drugs withdrawn and maintained normotension off medication at 12 months

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Study</th>
<th>Proportion*</th>
<th>RR</th>
<th>CI</th>
<th>P</th>
<th>Heterogeneity P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>[4] [24] [25] [26]</td>
<td>280/595</td>
<td>0.96</td>
<td>0.85–1.08</td>
<td>.51</td>
<td>.54</td>
</tr>
<tr>
<td>Female</td>
<td>[38] [39]</td>
<td>266/513</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight post WAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
<td>[7] [36] [42]</td>
<td>274/475</td>
<td>1.13</td>
<td>1.16–1.48</td>
<td>&lt;.001</td>
<td>.97</td>
</tr>
<tr>
<td>No weight loss</td>
<td>291/666</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium restriction post WAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>[7] [26] [42]</td>
<td>353/699</td>
<td>1.30</td>
<td>1.17–1.45</td>
<td>&lt;.001</td>
<td>.71</td>
</tr>
<tr>
<td>No</td>
<td>329/857</td>
<td></td>
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</tbody>
</table>

* Proportion with predictor who remained normotensive at 12 months after withdrawal of antihypertensive drugs. CI = confidence interval; other abbreviation as in Tables 1 and 3.
Committee on the Detection, Evaluation and Treatment of High Blood Pressure has recommended that the decision to treat mild-to-moderate BP elevation should be based on the results of at least two BP readings on at least three separate occasions.46

The importance of these recommendations was emphasized by the results of the Australian Therapeutic Trial in Mild Hypertension.47 Despite entry criteria that required a mean diastolic BP (from four recordings over two visits) in the range of 95 to 110 mm Hg, 48% of those randomized to placebo still decreased below this level during the 3 years of follow-up.

The subsequent availability of 24-h BP monitoring has also revealed the presence of white coat hypertension where BP, which becomes elevated during the stress of a medical encounter, returns to normal levels at other times.

The percentage of patients who are correctly started on therapy but who subsequently become normotensive is likely to be much smaller than the percentage where therapy was inappropriately commenced. However, it was notable in this review that adoption of appropriate lifestyle changes was identified as a consistent predictor of successful drug withdrawal. This is in keeping with the results of several major trials that have shown that a reduction in body weight, reduced salt and alcohol intake, and an increase in physical activity may be sufficient to reduce marginal BP elevations to normotensive levels.6 – 8,26,42

Because long-term compliance with such interventions is low, continued monitoring of BP is appropriate in these patients.

Few studies commented on the adverse effects of drug withdrawal, particularly rebound hypertension, which may accompany the sudden cessation of clonidine or the rebound hypersensitivity to adrenergic stimuli that accompanies sudden cessation of β-blockers.48,49 The latter is well characterized and may be incorrectly attributed to a recurrence of elevated BP. The symptoms, principally tachycardia in response to mild exertion, may lead to rebound angina and myocardial infarction and should be avoided by a slow and graded withdrawal of treatment. Programs that encourage drug withdrawal in selected patients should emphasize the importance of drug withdrawal symptoms and the strategy to avoid them.

Fig. 2 presents an algorithm designed to assist primary care physicians. This algorithm is derived from this systematic review and is intended as only a guide. It has not been tested on a clinical population and therefore, no formal estimates of success rates are provided. Patients who do not meet all of the criteria may still be suitable for drug withdrawal, although success is likely to be lower. The need to continue to attend regular BP checks should be emphasized to all patients, especially in the first 6 months. It is also recommended that behavioral modification be encouraged as clinical trials have shown that such interventions roughly double the rate of maintenance of normotension after withdrawal of antihypertensive drugs.6 – 8,26,42

The current recommendations by expert committees support periodic reassessment of drug therapy for hypertension for reduction in dosage and number of drug groups50 and withdrawal of antihypertensive drugs in certain circumstances with adequate follow-up.46,51,52

In conclusion, if antihypertensive medication is withdrawn from selected patients with mild-to-moderate hypertension, then approximately 42% of these patients are likely to remain normotensive for periods in excess of 12 months. The studies that have established this have had varying designs, patient populations, and even definitions of hypertension. Predictors of success have been identified in a number of these studies and would suggest the long-term well-controlled mild hypertensive patients on single agent therapy are appropriate candidates for a trial of withdrawal of antihypertensive medication, especially if they are willing to undertake lifestyle changes.

FIG. 2. Algorithm demonstrating a proposed sequence of decisions to determine which patients should be considered for withdrawal of antihypertensive drugs. Depth of box shading represents increasing likelihood of successful maintenance of long-term normotension. As lifestyle changes have been shown to double the rate of maintenance of normotension after withdrawal of antihypertensive drugs they should be offered to all patients in whom drug withdrawal or reduction is being contemplated. DBP = diastolic blood pressure; SBP = systolic blood pressure; BP = blood pressure; other abbreviation as in Fig. 1.
Acknowledgment

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References


