Primary care

Predictors of normotension on withdrawal of antihypertensive drugs in elderly patients: prospective study in second Australian national blood pressure study cohort

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Abstract

Objectives To identify simple long term predictors of maintenance of normotension after withdrawal of antihypertensive drugs in elderly patients in general practice.

Design Prospective cohort study.

Setting 169 general practices in Victoria, Australia.

Participants 503 patients aged 65-84 with treated hypertension who were withdrawn from all antihypertensive drugs and remained drug free and normotensive for an initial two week period; all were followed for a further 12 months.

Main outcome measures Relative likelihood of maintaining normotension 12 months after drug withdrawal; relative likelihood of early return to hypertension after drug withdrawal.

Results The likelihood of remaining normotensive at 12 months was greater among younger patients (65-74 years), patients with lower "on-treatment" systolic blood pressure, patients on single agent treatment, and patients with a greater waist:hip ratio. The likelihood of return to hypertension was greatest for patients with higher "on-treatment" systolic blood pressure.

Conclusions Age, blood pressure control, and the number of antihypertensive drugs are important factors in the clinical decision to withdraw drug treatment. Because of consistent rates of return to antihypertensive treatment, all patients from whom such treatment is withdrawn should be monitored indefinitely to detect a recurrence of hypertension.

Introduction

A systematic review of predictors of maintenance of normotension after withdrawal of antihypertensive drugs indicated that if treatment is withdrawn from selected patients with mild to moderate hypertension then approximately 42% of these patients are likely to remain normotensive after 12 months.[1] Predictors of success for maintenance of normotension have been identified in these studies and indicate that patients with long term, well controlled, mild hypertension on single agent antihypertensive treatment are optimal candidates for a trial of withdrawal of antihypertensive drugs, especially if they are also willing to undertake appropriate lifestyle changes.

We report the experience of withdrawal of antihypertensive drugs in 503 patients aged 65-84 years in a cohort study conducted in an Australian general practice setting and identify characteristics of patients that predict successful maintenance of normotension over a 12 month period. The study was novel in prospectively investigating predictors of successful antihypertensive drug withdrawal for elderly patients that are likely to be useful to a general practitioner in routine clinical practice.

Methods

We used a prospective cohort design to investigate predictors of persistent normotension 12 months after withdrawal of antihypertensive drug treatment. We used participating general practitioners' databases to identify suitable participants—patients aged 65-84 years with a history of treated hypertension. We drew participants from among patients volunteering for inclusion in the second Australian national blood pressure study. This was a large randomised controlled trial comparing angiotensin converting enzyme inhibitor and diuretic based antihypertensive treatment for major cardiovascular outcomes and all cause mortality.[2] Patients taking antihypertensive drugs at screening were offered withdrawal of drugs as part of the run-in phase. Pretreatment blood pressure could not be identified for all participants, so hypertensive status relied on self reporting. Patients who returned to hypertension were eligible for enrolment in the second Australian national blood pressure study.

Patients who agreed to participate had their previous antihypertensive drug treatment withdrawn gradually under the supervision of a research nurse. During the drug withdrawal phase participants were seen weekly for blood pressure monitoring until a minimum of two weeks after cessation of all antihypertensive drugs. Only those patients whose blood pressure remained within the normotensive range at the two week post-withdrawal visit entered the present study. We defined "normotension" as a sitting systolic blood pressure below 160 mm Hg and a diastolic pressure below 90 mm Hg. These criteria are now historical as they were established before the first patient entered

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Table 1 Baseline characteristics according to blood pressure classification at 12 months. Values are numbers (percentages unless stated otherwise)

Characteristic	"Maintain normotension" (n=181)	"Return to hypertension" (n=273)	"Return to hypertension early" (<70 days) (n=135)	"Return to hypertension late" (≥70 days) (n=138)
Sex:				
Female	95 (52.5)	161 (59.0)	72 (53.3)	89 (64.5)
Male	86 (47.5)	112 (41.0)	63 (46.7)	49 (35.5)
Median (range) age (years)	70.0 (65.0-84.0)	71.0 (65.0-84.0)	72.0 (65.0-84.0)	71.0 (65.0-82.0)
Mean (SD) pretreatment blood pressure (mm Hg):				
Systolic	169.8 (20.0)	169.4 (18.1)	171.6 (17.7)	167.5 (18.4)
Diastolic	93.7 (10.2)	94.5 (9.6)	94.6 (9.7)	94.5 (9.6)
Mean (SD) on-treatment blood pressure (mm Hg):				
Systolic	135.3 (13.0)	141.4 (13.6)	143.5 (13.4)	139.3 (13.5)
Diastolic	76.0 (8.9)	77.0 (7.8)	77.5 (7.9)	76.5 (7.8)
Mean arterial	95.7 (8.9)	98.4 (8.3)	99.5 (8.0)	97.4 (8.6)
Pulse pressure	59.3 (11.6)	64.4 (12.1)	66.0 (12.8)	62.9 (11.2)
Other cardiovascular disease risk factors:				
Mean (SD) body mass index (kg/m^2)	26.9 (3.4)	27.3 (4.1)	27.0 (4.0)	27.5 (4.2)
Mean (SD) waist:hip ratio	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)
Raised cholesterol concentration	102 (56.4)	118 (43.2)	49 (36.3)	69 (50.0)
Diabetes mellitus	16 (8.8)	20 (7.3)	11 (8.1)	9 (6.5)
Smoker	13 (7.2)	12 (4.4)	8 (5.9)	4 (2.9)
Family history of heart disease	99 (54.7)	145 (53.1)	67 (49.6)	78 (56.5)
Personal history cardiovascular disease*	42 (23.2)	47 (17.2)	22 (16.3)	25 (18.1)
Previous single drug treatment	141 (77.9)	173 (63.4)	84 (62.2)	89 (64.5)
Mean (SD) plasma creatinine (μmol/l)	86.1 (16.9)	88.5 (22.1)	89.4 (21.4)	87.7 (22.8)
Alcohol intake:				
Heavy	64 (35.4)	81 (29.7)	41 (30.4)	40 (29.0)
Moderate	83 (45.9)	95 (34.8)	49 (36.3)	46 (33.3)
Never drink	28 (15.5)	78 (28.6)	36 (26.7)	42 (30.4)
Recent exercise	166 (92.7)	236 (90.1)	116 (89.2)	120 (90.9)

*Angina, claudication, stroke, myocardial infarction, coronary artery bypass grafting, or coronary angioplasty.

the second Australian national blood pressure study in early 1995. However, in previous studies the level of defined hypertension did not alter the success of drug withdrawal.[1]

Candidate predictors of maintenance of normotension included body mass index, waist:hip ratio, blood pressure (on-treatment diastolic and systolic), heavy or higher weekend (binge) alcohol intake, recent exercise (walking or other vigorous activity), number of antihypertensive drugs taken, sex, and age. We selected these potential predictors on the basis of previous studies and ready availability to a general practitioner.

After a minimum of two visits to the nurse after cessation of all antihypertensive drugs, participants were followed up by their general practitioner. Typically, general practitioners reviewed each participant 10 times during the subsequent 12 month period (range 1-56 reviews) and recorded blood pressure on four or five occasions (range 0-29 recordings). We reviewed the clinical notes of all participants six and 12 months after withdrawal of treatment and extracted data on blood pressure, drugs, and adverse cardiovascular events. A research nurse measured participants' sitting blood pressure with a standard sphygmomanometer at a 12 month visit.

Twelve months after their entry into the study we classified patients into three groups: (1) Remained off antihypertensive treatment and were normotensive at the 12 month visit ("maintain normotension"). (2) Met study criteria for return to hypertension according to measurement by the study nurse (seated systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥90 mm Hg where systolic blood pressure ≥140 mm Hg)

or had restarted antihypertensive treatment because of a blood pressure level that the general practitioner considered to justify reinstitution of treatment at or before the 12 month visit ("return to hypertension"). We also analysed this group as "return to hypertension early" (<70 days) and "return to hypertension late" (≥70 days). (3) Restarted antihypertensive treatment for reasons unrelated to blood pressure or died before classification—this group is referred to as "other."

Statistical analysis

We assessed the relation between potential predictors and normotensive status at 12 months by using Cox's proportional hazards regression in order to estimate relative risks, using a constant follow up time of one year with robust estimation of variance to account for clustering within doctor.[3] [4] We used a multivariate model to determine independent predictors, after standardising continuous predictors to account for differences in scale. We used SAS version 8.2 for all analyses.

Results

The study population consisted of 503 participants, all of whom had remained normotensive for at least two weeks after withdrawal of all antihypertensive drug treatment. All but five participants were followed according to the protocol and reviewed 12 months after study entry. At this time 181 (36%) were classified as "maintain normotension," 273 (54%) as "return to hypertension," and 49 (10%) as "other." Four participants had died during the interim period, two from
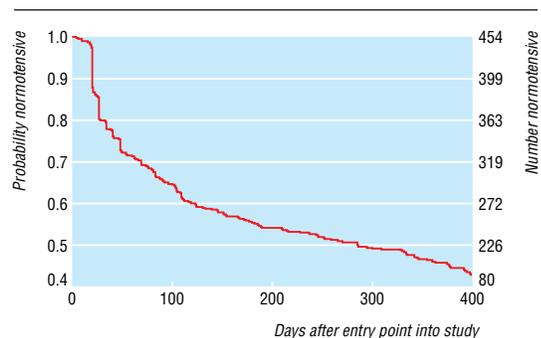
Survival plot of participants' (n=454) normotensive status over a 12 month period after cessation of antihypertensive treatment. Participants classified as "other" (n=49) were excluded from this analysis

cancer and two with vascular events. The remaining unclassified participant was known to be alive and not taking antihypertensive drugs at 12 months. In most instances, drug treatment in "other" participants was restarted because of ankle swelling (18) or heart failure (8). Table 1 contrasts the baseline characteristics of the "maintain normotension" and "return to hypertension" groups, as classified at 12 months after study entry.

Table 2 shows the results of a multivariate analysis conducted to determine a set of independent predictors of maintenance of normotension. These are expressed as risk ratios, with "return to hypertension" as the comparison group. In both "return to hypertension" and "return to hypertension early" lower on-treatment systolic blood pressure was the major predictor. Other predictors were younger age (65-74 years), greater waist:hip ratio, and the use of a single antihypertensive drug.

The figure shows the proportion of the study population who remained normotensive at various times after drug withdrawal. It indicates that as many participants returned to hypertension in the first 70 days as in the subsequent 330 days. The probability of return to hypertension between 200 days and 400 days was 0.11.

Discussion

A relatively high percentage (37%) of participants remained normotensive one year after drug withdrawal in this study. This finding has been replicated in other major studies and is similar to the 42% in our systematic review.[1 5 6–13] The figure shows that although most patients who returned to hypertension did so in

the first 100 days after entry into the study, the rate thereafter was constant. Thus long term systematic follow up is needed for patients who are offered this strategy in clinical practice.

This study has identified patient characteristics that predict the likelihood of successful antihypertensive drug withdrawal among patients treated in a general practice setting. The patients selected were elderly (over 65 years) and had blood pressure levels judged to allow a brief period of safe drug withdrawal before entry into the second Australian national blood pressure study. The distribution of blood pressures is likely to have been similar to that of typical patients with mild to moderate hypertension encountered in general practice, which is reflected in the high number of patients on single drug treatment before drug withdrawal (table 1).

The study identified several predictors of sustained normotension as well as early return to hypertension. All of these were among a series of simple clinical variables prospectively chosen as likely to be routinely available to guide a general practitioner's clinical management.

Study design

Certain limitations of the study design require comment. In the first place, the study was largely observational and relied on judgment by doctors both for starting antihypertensive treatment and for determining whether it was appropriate to restart treatment. Doctors vary in their thresholds for initiating treatment and are also encouraged to use different thresholds according to the level of integrated cardiovascular risk in individual patients.[14] However, in all cases return to antihypertensive drug treatment was initiated by the patients' general practitioner as "the most appropriate" course of action for the individual patient.

Another limitation is the natural variability of blood pressure and its likelihood of being transiently elevated—for example, by alcohol intake, other drugs, or fluctuations in body weight.[15 16] Predictors of successfully sustained normotension may also have a complex relation to their outcome variable. For example, they may reflect factors that have led to more frequent than normal measurement of blood pressure or a lower threshold for introduction of treatment (such as other illnesses or the presence of other cardiac risk factors); factors that have led to a transient elevation of blood pressure that has subsequently resolved or an exaggerated white coat effect (a transient period of excessive alcohol intake or increase in body weight); or factors that are associated with

Table 2 Characteristics that are independent predictors of "maintain normotension" status 12 months after withdrawal of all antihypertensive drugs versus "return to hypertension." The results for "return to hypertension early" were very similar

Characteristic	Univariate analysis		Multivariate analysis	
	Relative risk (95% CI)	P value	Relative risk (95% CI)	P value
On-treatment systolic blood pressure (10 mm Hg increase)	0.82 (0.75 to 0.89)	<0.001	0.85 (0.81 to 0.89)	<0.001
Age (years):				
65-74	1.61 (1.16 to 2.24)	0.005	1.57 (1.13 to 2.17)	0.007
75-84	1.00		1.00	
Waist:hip ratio (0.1 unit increase)	1.12 (0.98 to 1.28)	0.11	1.22 (1.12 to 1.32)	0.02
Single drug treatment	2.44 (1.54 to 3.85)	<0.001	2.38 (1.50 to 3.76)	<0.001
Two or more drugs	1.00		1.00	

an increased likelihood of success of non-pharmacological blood pressure reduction.[8 13] Alternatively, treatment may have been introduced inappropriately because of poor measurement technique, too few blood pressure measurements, or a failure to initiate behaviour modification before introducing drug treatment (misclassification error).[15 16]

Utility of predictors

The predictors identified in this study probably fit into several of these categories. On-treatment systolic blood pressure is likely to correlate with the true pretreatment blood pressure and is therefore a plausible predictor of successful withdrawal. Younger patients may be more often started on treatment inappropriately because of an exaggerated white coat effect, so younger age is a plausible predictor of successful withdrawal. A low waist:hip ratio may predict earlier return to treatment because doctors have less opportunity to encourage non-drug treatments (in particular weight loss), or patients with a higher waist:hip ratio may lose weight and delay return to hypertension.[1] Single drug treatment reflects the mild nature of the blood pressure off treatment and is therefore a plausible predictor.

Considering the strength of the predictors and their plausible relations to successful antihypertensive drug withdrawal, it is likely that only a minority of the candidate predictors will be useful in a clinical setting. The most relevant predictors of successful withdrawal are younger age (65-74 years), relatively low on-treatment systolic pressures, and minimal drug treatment. Conversely, those least likely to be successful are older patients with higher on-treatment pressures and two or more antihypertensive drugs. The systematic review found that the most consistent predictors identified among the included studies were blood pressure (lower pretreatment, on-treatment, and post-withdrawal), pharmacotherapy (fewer agents and lower dose), and dietary intervention (weight and sodium reduction).[1]

The predictive power of each of the identified factors was relatively modest, ranging from 0.85 to 2.38. The ability of the model to predict maintenance of normotension versus return to hypertension was 41% of maintenance of normotension correctly predicted, 83% of return to hypertension correctly predicted, and 66% correct overall. The ability of the model to predict maintenance of normotension versus "early" return to hypertension was 90% of maintenance of normotension correctly predicted, 38% of early return to hypertension correctly predicted, and 68% correct overall. Thus identified predictors for maintenance of normotension are most useful in the first 70 days after drug withdrawal.

The ability of the model with on-treatment systolic blood pressure only to predict maintenance of normotension versus return to hypertension was 16% of maintenance of normotension correctly predicted, 91% of return to hypertension correctly predicted, and 61% correct overall. On-treatment systolic blood pressure is therefore the single most useful measure to exclude patients from a trial of antihypertensive drug withdrawal.

However, other more powerful predictors may exist. Given the wide range of simple measurements in

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What is already known on this topic

Systematic reviews have identified predictors of success of withdrawal of antihypertensive medication

The reviewed studies have mainly been in a hospital or specialist clinic setting, and their recommendations may not be practical in general practice

What this paper adds

This study has identified simple predictors of success that are readily available to general practitioners

On-treatment systolic blood pressure, the number of blood pressure lowering drugs, and the age of the patient are reliable indicators of who may successfully stop taking their drugs

General practitioner practitioners should not be dissuaded from offering drug withdrawal to patients with greater waist:hip ratios

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this study, future studies could test physiological measures such as arterial compliance and pulse wave velocity at baseline as clinical tests to predict maintenance of normotension. Left ventricular hypertrophy, for example, has been previously identified as an important predictor.[17]

Systematic follow up of all patients offered withdrawal of antihypertensive drug treatment is mandatory. As the rate of return to hypertension is greatest at the time of cessation, a reasonable regimen would be weekly visits for two weeks, then fortnightly visits for two months, and then monthly visits for six months. Beyond this time, six monthly visits should continue indefinitely. This strategy should be offered only to patients with uncomplicated hypertension—that is, no cardiovascular disease or comorbidity for which the treatment is also needed.

Conclusion

In view of the substantial cost of antihypertensive treatment, the findings of this study emphasise the value of a trial of withdrawal of antihypertensive treatment with systematic follow up in patients who fit the profile of younger (65-74 years) age with blood pressure well controlled on relatively minimal treatment.

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