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Maximizing the benefit of treatment in mild hypertension: three simple steps to improve diagnostic accuracy

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Summary

Background: Most patients only have three measurements of blood pressure before being labelled as hypertensive. This may lead to inaccurate classification, unnecessary treatment and dilution in treatment benefit for the population.
Aim: To examine the accuracy of current methods of diagnosing mild hypertension, and to explore ways to improving targeting of antihypertensive treatment without entailing lengthy observation.
Design: Re-analysis of published data.
Methods: We tested current diagnostic methods using the data for 3965 individuals who were followed for a year in the placebo arm of the MRC Mild Hypertension Trial. We calculated the proportion selected for treatment by current methods and the diagnostic accuracy, using average blood pressure beyond 6 months as representing 'true' long-term blood pressure. We examined the benefit of averaging blood pressures, of prolonging observation modestly and of estimating within-person blood pressure variability.
Results: Prolonging observation to 3 months selects a smaller (by about 12%) proportion of the sample for treatment, a proportion similar to that defined as 'truly' hypertensive. The diagnostic accuracy of current methods is poor, with up to 69% discrepancy in classification. This discrepancy was improved by up to 18% in absolute terms by prolonging observation to 3 months and using average blood pressures. Identifying those individuals with low within-person variability allows marked improvement in the prediction of 'true' hypertension.
Discussion: Although some inaccuracy in the diagnosis of hypertension is inevitable, observation for 3 months, averaging blood pressures and estimating within-person blood pressure variability can markedly improve upon current practice.

Introduction

Current guidelines for the management of hypertension[1] recommend prolonged observation of patients with mild hypertension before initiation of treatment. The main reason for this is the notion that 'falsely hypertensive' patients will be 'weeded out', and unnecessary treatment avoided. However, the guidelines do not specify the precise length of observation needed, nor do they advise whether the

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last single measurement obtained or the average of several should be used for decision-making. Data from the UK in the early 1990s suggested that doctors treating hypertensives did not follow the guidelines, as up to 90% of those labelled hypertensive had fewer than three measurements before the diagnosis was made.[2,3] This practice appears not to have improved recently,[4–6] and the implementation of guidelines may not have had the hoped-for impact on patient outcomes.[7] We thus still need simple and speedy methods for improving classification of individuals, which also would benefit society as a whole.

The current practice in labelling of hypertensives is not very different from the selection procedure used in the MRC trial of treatment in mild hypertension,[8] and in this study we have examined how accurate current practices[2,3] are in the diagnosis of mild hypertension, by applying them to the placebo arm of the MRC trial database. We suggest three simple steps that would improve the targeting of antihypertensive treatment without the need for lengthy observation.

Methods

Study population

We had available the first year's blood pressures for 8654 individuals in the placebo arm of the MRC trial, of whom 3965 had complete follow-up data and were included in the current analysis. In the MRC trial,[8] blood pressure was measured in existing urban GP clinics by trained observers, using Hawksley random zero sphygmomanometers, thus minimizing technique-related errors and observer bias. Four assessments of blood pressure were made before randomization, the average of the first two being entered as the 'screening' pressure and the average of assessments 3 and 4 as the 'entry' pressure. Individuals were included in the study if 'entry' diastolic blood pressure was 90–109 mmHg and systolic blood pressure < 200 mmHg. Follow-up visits were at weeks 2, 4, 6, 8, 10, 12, 26, 39 and 52.

For the purpose of this analysis, we have chosen diastolic blood pressure ≥ 90 mmHg or ≥ 100 mmHg, and systolic blood pressure ≥ 160 mmHg as denoting hypertension. To represent current practices for diagnosing hypertension, we chose follow-up blood pressure at week 2 (third blood pressure in database, but in fact the fifth visit). As average blood pressure correlates better than single readings with target organ damage,[9] and no guidelines advise observation beyond 6 months, we have selected the average blood pressure of three visits at weeks 26, 39 and 52 as representing 'true' long-term blood pressure (i.e. beyond 6 months).

Proportion of sample selected for treatment

First, we looked at the proportion of the total sample that would be selected for treatment according to the above defined thresholds if current practices[2,3] were applied to the database. Second, we looked at the proportion that would be selected for treatment by the average blood pressure of the last three visits after 3 months observation. Both methods were then compared to the proportion of the sample that was 'truly' hypertensive (i.e. according to average blood pressure beyond 6 months).

Diagnostic accuracy

Clinic blood pressure exhibits considerable within-person variability, and thus even though the overall percentage of hypertensive subjects may be constant, each individual might be classified as hypertensive at one particular time point but normotensive at another (and vice versa). We looked at the extent of this by calculating the diagnostic accuracy for (i) current practices and (ii) classification based on the average blood pressure of the last three visits after 3 months observation. The diagnostic accuracy was defined as the percentage of individuals in a category initially that fell into the same category at a second assessment. The second reference assessment was the 'true' long-term blood pressure beyond 6 months.

Probability of 'true' hypertension

It would be helpful if it were possible to identify early (and easily) subgroups of individuals who were most likely not to change their blood pressure in the long term (i.e. those with low within-person blood pressure variability). To this end, we calculated the probability of 'true' long-term hypertension, using diastolic blood pressure ≥ 100 mmHg to define hypertension, as this is an universally accepted indication for pharmacological treatment.[10–12] We first calculated the probability of long-term hypertension as predicted by current practices, and then as predicted by average blood pressure after 3 months follow-up, combined with low within-person blood pressure variability.

As a measure of within-person variability in blood pressure, we calculated the coefficient of variation (CV) for the blood pressure values obtained at the last 3 visits after 3 months observation period ($CV_{BP} = SD/mean \times 100$). The bottom quartile of

Table 1 The proportion of the sample selected for treatment by current GP practice, and by mean blood pressure (BP) after 3 months, compared to the 'true' proportion of hypertensives*

Threshold	Current practice	Mean BP after 3 months	'Truly' hypertensive*
DBP $\geq$ 90 mmHg	67.6 $\pm$ 1.5	55.5 $\pm$ 1.6	57.8 $\pm$ 1.5
DBP $\geq$ 100 mmHg	24.9 $\pm$ 1.4	13.8 $\pm$ 1.1	12.5 $\pm$ 1.0
SBP $\geq$ 160 mmHg	25.9 $\pm$ 1.4	15.4 $\pm$ 1.1	18.5 $\pm$ 1.2

Data are percentages $\pm$ 95%CIs. DBP, diastolic blood pressure; SBP, systolic blood pressure.
*See Methods for definition.

CV_{BP} defined those individuals with the lowest within-person variability in blood pressure.

Results

Proportion of sample selected for treatment

The proportion of the sample selected for treatment depended on the threshold chosen and length of observation (Table 1). Current practices of initiating hypertension treatment at or before obtaining three blood pressure values, select a significantly larger proportion (about 10–12%) of the sample for treatment, than would be selected by follow-up beyond 6 months. However, simply prolonging observation to 12 weeks and using the average of the last three visits, selected a very similar proportion for treatment as would have been selected if the observation time had been prolonged to beyond 6 months.

Diagnostic accuracy

For current practices, the accuracy of diagnosis varied from 31% to 92% (Figure 1), depending on the threshold chosen, and whether the analysis was done for pressures initially higher or initially lower than the threshold. This means that the currently widespread practice of initiating treatment after only three visits may lead to unnecessary treatment in up to 69% of individuals (for $\geq$ 100 mmHg diastolic initially). There was an absolute improvement in classification discrepancy rates of up to 18% from prolonging observation to 3 months and using average of the last three visits for classification. The greatest improvement was noted for pressures initially higher than the thresholds. However, diagnostic accuracy remained fairly poor in spite of this improvement. For example, only 47% of individuals initially with average diastolic blood pressure $\geq$ 100 mmHg remained in that category after 1 year of observation, and in fact this figure does not improve with longer follow up, e.g. comparing week 39 with week 52 (data not shown).

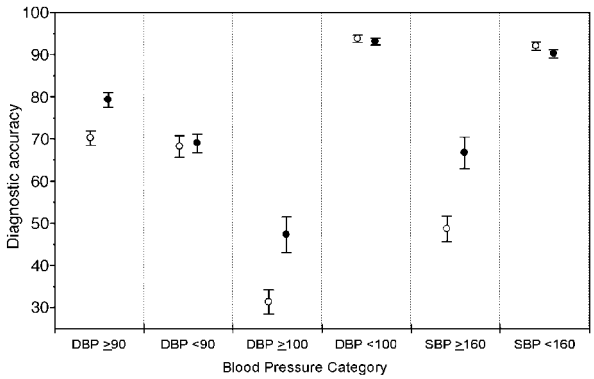

Figure 1. Diagnostic accuracy (see text for definition). Open symbols relate to current GP practices. Closed symbols indicate the accuracy if average blood pressure of the last three visits of 3 months observation was used for diagnosis. DBP, diastolic blood pressure; SBP, systolic blood pressure (both in mmHg). Error bars indicate 95%CIs.

Probability of 'true' hypertension

Median CV_{BP} was 5.0, with the 25th percentile at 3.1. For current practices, the probability of 'true' hypertension (long-term diastolic blood pressure $\geq$ 100 mmHg) was 0.23 if initial diastolic blood pressure was in the range 100–104 mmHg (Figure 2). Prolonging the follow-up period to 3 months and using average blood pressure in combination with low within-person variability ($CV_{BP} < 3.1$), increased the probability to 0.40 for initial diastolic blood pressure in the range 100–104 mmHg. It can be seen from Figure 2 that the higher the initial blood pressures, the higher the probability of long-term blood pressure remaining $\geq$ 100 mmHg. However, the probability remains at best about 0.43 for current GP practices, and is at best about 0.70 for those who have low within-person variability and average initial (here, although actually the fifth visit) blood pressure $\geq$ 112 mmHg.

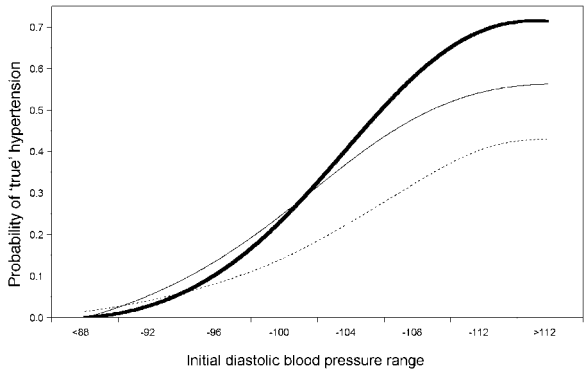

Figure 2. 'True' hypertension is defined as diastolic blood pressure ≥100 mmHg beyond 6 months of follow-up. The dotted line indicates the probability of correct diagnosis according to methods currently used for ranges of blood pressure as indicated. The thin solid line indicates the probability calculated by using average blood pressures from the last three visits of 3 months follow up, while the thick solid line represents the same group but now including only those with $CV_{BP} < 3.1$ (25th percentile).

Discussion

Life-long treatment with several drugs usually follows the diagnosis of hypertension. This diagnosis therefore needs to be as accurate as possible. The MRC trial of mild hypertension, defined as systolic blood pressure < 200 mmHg and diastolic blood pressure of 90–109 mmHg, showed that 850 individuals need to be treated for one year in order to save one stroke (so-called number needed to treat, NNT)—a very high figure compared to some other forms of primary cardiovascular disease prevention.[13,14] However, this figure is probably an underestimate of the potential benefit of antihypertensive treatment, caused by the brief selection procedure, and could be lowered with more careful and better targeting of patients.[15]

At present, the majority of those labelled as hypertensive have had only 2–3 estimates of their blood pressure before the initiation of antihypertensive treatment,[2,3] which is broadly comparable to the selection procedure used in the MRC trial of mild hypertension.[8] In this paper, we have applied current methods of diagnosing hypertension to the placebo arm of the MRC trial, and found that this leads to very poor targeting of treatment.

Considering the treatment threshold of ≥100 mmHg diastolic, current methods not only select an excessive proportion of the population for treatment (by 10–12%, Table 1), but also incorrectly classify up to 69% of the individuals (Figure 1). Better targeting would lower NNT, as is recognized by current guidelines[8,16] recommending prolonged observation for up to 6 months. However, we believe that 6 months is unduly long, risking loss to follow-up, and previous estimates have suggested that blood pressure in populations does not change much beyond 3–4 months[16] or after six separate visits.[17] The analysis presented here shows that if blood pressure is assessed eight times over only 3 months and the average of the last three visits is used for classification, then the proportion of the sample selected for treatment is similar to that after a whole year's follow-up (Table 1). This initial fall in the proportion selected for treatment is most likely due to regression to the mean, and habituation to repeated measurements. With still longer follow-up, there may be minor fluctuations in the percentage selected for treatment in such a large sample, but the clinical relevance of those is doubtful.

A major corollary of the current analysis is that although the proportion of the population selected seems to have reached equilibrium at 3 months, we are not selecting the same individuals for treatment at different time points. Thus the diagnostic accuracy of current methods for initial diastolic blood pressure ≥100 mmHg was only 31% (69% of those patients are not 'truly' hypertensive, see Figure 1). The diagnostic accuracy is in reality likely to be even lower, since in the MRC-trial, observer bias and technique-related errors have been minimized, and the blood pressure in the database used to represent the value GP's currently act on was in fact the fifth visit in the trial. Our suggestion, to prolong observation to 3 months, resulted in a considerable improvement (up to 18%) in the diagnostic accuracy, but accuracy was still poor, for example, for those initially with diastolic blood pressure ≥100 mmHg (Figure 1). The population studied was selected on the basis of blood pressures being higher than the population average, and therefore part of the discrepancy in classification will be explained by regression to the mean, e.g. for blood pressures higher than the threshold chosen. However, the inherent blood pressure variability of each individual also plays a role, and given the continuous blood pressure distribution in the population, a degree of imprecision in the diagnosis of hypertension is inevitable.

It is not surprising that those with blood pressure much higher than the treatment threshold are more likely to remain in that category, i.e. being correctly identified as hypertensive. However, the probability of being correctly identified as hypertensive is at best about 0.4 if current methods in General Practice are used (Figure 2). We can improve markedly on this by prolonging observation to 3 months, using average blood pressures and

calculating CV_{BP}. Those exhibiting very low intrapersonal variation in blood pressure (solid thick line in Figure 2) as defined by $CV_{BP} < 3.1$, still represent 25% of the individuals in the MRC trial. In spite of this marked improvement in the prediction of sustained hypertension, the probability of correct identification is still at best only about 0.7. Calculation of CV_{BP} is a simple and quick task, using a modern calculator, most of which have an automatic facility for calculating standard deviation.

Implicit in the results of this analysis is an observation that we require better methods for diagnosing mild hypertension. Ambulatory blood pressure monitoring allows collection of multiple readings without the potential loss to follow-up that is seen in clinical practice. Reproducibility of ambulatory blood pressure monitoring is reported to be twice that of clinic measurement,[18] is not subject to habituation to repeated measurements[19] and identifies the problem of 'white coat' hypertension.[20] The improved precision of this technique may thus lead to a more rapid identification of those patients with 'true' hypertension who would benefit most from anti-hypertensive therapy.[21] While ambulatory blood pressure monitoring may at present be beyond the reach of most primary practitioners, self monitoring of blood pressure at home is an alternative,[22] or one can adopt these three simple steps, which can markedly improve on current practices used for targeting antihypertensive treatment: (i) assessment of blood pressure eight times over 3 months; (ii) classification of patients using the average blood pressure of the last three visits; and (iii) estimation of within-person blood pressure variability by calculation of coefficient of variation.

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