A Fresh Approach to the Evaluation of Antihypertensive Agents

D. BRUCE CAMPBELL, SARA LOWE, DOUG TAYLOR, PAUL TURNER, AND NICOLA WALSH

SUMMARY  Clinical studies on the use and activity of drugs often rely on data generated from a relatively small number of patients, and definitive conclusions are drawn that are assumed to represent the population at large. Similarly, interpretation and comparison of studies are made difficult when end points of effectiveness, particularly with antihypertensive agents, are arbitrarily chosen. The results from a clinical study of more than 1400 hypertensive patients after indapamide therapy for 3 months, alone or in combination with a beta blocker, are presented using a different graphic approach. This is based on the assumption that the magnitude of the fall in blood pressure after hypertensive therapy is dependent on initial blood pressure. Diastolic and systolic pressures were plotted as a scattergram against the change in blood pressure. Predetermined response lines were drawn with a slope of 1 and intercepts on the initial blood pressure axis of 90 mm Hg for diastolic and 140 mm Hg for systolic pressures with tolerance limits of ± 10 mm Hg drawn about it. Subdivisions of response can be achieved by counting the number of patients above and below these lines. This allows a drug to be "finger-printed" in terms of its pattern of activity in all degrees of severity of hypertension and, more relevant, direct comparisons with other drugs can be made. Similarly, the potential activity of the drug can be determined by computing the slope and intercept of the actual regression line through the data points. Using this approach, indapamide, at a fixed dosage of 2.5 mg/day, was shown to be an effective antihypertensive agent in all degrees of hypertension, in young and elderly patients.

This analytical approach can also be used for other therapeutic classes of drugs.

(Hypertension 7 [Suppl II]: II-143-II-151, 1985)

KEY WORDS  • indapamide  • data presentation  • regression analysis  • efficacy assessment

THE need to treat both asymptomatic and symptomatic hypertensive patients is now incontestable after publication of three long-term studies.1-3 Both fatal and nonfatal events of cerebrovascular accidents and congestive heart failure were found to be reduced significantly, but the smaller reduction in coronary heart disease could not be fully explained and may be due to the use of old and even obsolete drugs in some of these studies. The choice of therapy, which may be given to 10 to 20% of the population for the duration of their life, is not self-evident. Indeed, little progress has been made to choose a particular drug with a particular well-researched mechanism of action for a particular patient or even a population subgroup according to pathophysiological profile.

With the ever-increasing number of new drugs becoming available, it is impossible and now unethical to test them all in long-term, placebo-controlled studies or compare them with existing drugs for a reduction in morbidity and mortality. Most investigators have to rely on the short-term blood pressure measurements over a few weeks and rarely for more than a few months. Although the actual measurement of blood pressure is relatively simple, it does require some consideration in terms of the choice of techniques and indexes (diastolic, systolic, or mean pressure).

More of a problem, however, is the use and presentation of these data, since end points and measurements of effectiveness tend to be chosen arbitrarily to suit the study and the results that are required. A review of the literature reveals that several end points are used. Typically, effectiveness is considered to be achieved if a certain number of patients produce a predetermined but arbitrarily chosen percentage drop in diastolic or mean blood pressure, or a drop to less than 90 or 95 mm Hg irrespective of age or initial blood pressure. Similarly, investigators may use qualitative...
categorization of results, for example, excellent, good, or poor response, but the rationale for choosing such categories is rarely explained. Statistical differences between placebo and another therapy can also be sought, but these may have little clinical significance. Another problem is that it is impossible to compare all antihypertensive agents; thus comparisons with standard drugs are made, but unless the size of the study is large, statistical differences may not be found. The patients have normally mild or moderate hypertension with diastolic pressure of not more than 115 mm Hg, and unless the drug under test is completely inactive, a fall to 90 to 95 mm Hg can be expected; a greater fall is unlikely and could even be undesirable. Mean overall drops of systolic and diastolic blood pressures are quoted to compare one study to another or to indicate superiority of a particular drug over another, but unless the groups of patients are similar, for example, in terms of equivalent dosage used, initial blood pressure, age, and racial group, these comparisons may be uninterpretable.

We describe a method of handling and presenting data from antihypertensive studies, particularly where large numbers of patients are involved and a wide range of initial blood pressures is encountered, allowing a more objective assessment of the usefulness of a drug. The procedures were based on those devised by Dixon and Johnson, but were extended to incorporate systolic pressures and statistical and graphic representations of the data. We used the data from a large multicenter study involving general practitioners administering indapamide, alone and in combination with other drugs, to a total of 2497 patients. Details of the methods and a simplified analysis of the data have been previously reported, but only results from patients treated with indapamide alone (473 newly diagnosed, 729 previously treated) or in combination with previous beta blocker treatment (365 patients) are given here.

Methods

We used the data from a large multicenter study involving general practitioners administering indapamide, alone and in combination with other drugs, to a total of 2497 patients. Details of the methods and a simplified analysis of the data have been previously reported, but only results from patients treated with indapamide alone (473 newly diagnosed, 729 previously treated) or in combination with previous beta blocker treatment (365 patients) are given here.

Study Design

The study design was open, but controlled by a 4-week run-in period for existing therapy, if any. At the start of this period, patients were screened and only those with blood pressures equal to or greater than 140/90 mm Hg were included. Entry data of age, weight, pulse, blood pressure, and existing therapy were recorded. After a month, the baseline measurements were taken and existing therapy was either continued with the addition of indapamide (2.5 mg daily) or replaced by indapamide. Patients were seen at 1-month intervals for 3 months when blood pressure, pulse, weight, and medication changes were recorded. Blood pressure measurements were always taken in the sitting position after a rest period of not less than 5 minutes, and Korotkoff phase 5 was recorded as the diastolic pressure.

Quantitative Analysis

Mean blood pressures were initially plotted against time to show the magnitude of the drop in pressure (Figure 1) over the 3-month treatment period.

Analysis of Variance

The difference between treatment periods and baseline were investigated by two-way analysis of variance (ANOVA) tests. If statistical differences were detected, this was followed by a Tukey's multiple range test to find where the differences lay (Table 1).

Correlation Analysis

Assuming that the drug significantly reduced blood pressure, a least square regression analysis was performed on baseline versus fall in blood pressure at each month, and the slope, intercept, and the correlation coefficient r calculated for indapamide alone and in combination with a beta blocker. In addition, a regression analysis was carried out on age and fall in diastolic blood pressure.

Qualitative Analysis — Predetermined Response Line

The procedure described by Dixon and Johnson assumes that there is a direct positive relationship between initial blood pressures and the magnitude of their fall for each individual patient after drug treatment, provided that the side effects do not restrict titrating the dose, when necessary, for severely hypertensive patients. The baseline diastolic blood pressures were plotted as a scattergram against the change in blood pressure. A predetermined response line was drawn with a slope of 1 and an intercept on the x axis of 90 mm Hg with tolerance limits of ±10 mm Hg drawn about the line (see Figure 1). These limits were based on the assumption of a 5-mm Hg error in blood pressure measurement and did not relate to the confidence limits or uncertainty of the construction of the regression line. If all points fell upon this line, it would indicate the unlikely situation that the drug was ideal and all patients' blood pressure was reduced to 90 mm Hg; in practice some patients will be above the line, indicating good response, or below the line, indicating poor response. Further subdivision of response can be achieved with the ±10-mm Hg limits around this line, providing excellent, good, acceptable, and poor categories (Figure 2) by counting the number of patients falling within these bands.

The basic method was extended to the analysis of systolic pressure, with a predetermined response line with a slope of 1 intercepting the axis at 140 mm Hg. In this study, both age and severity of starting diastolic blood pressure were considered important areas for investigation, and as group sizes were large (more than 100), the method was also used to investigate these subgroups. At each time point, two age subgroups were analyzed based on the British retirement age for men (less than 65 years and 65 or older) as well as the total group. The results for those 65 years and older (n = 372, 52% of the whole group) were investigated using a predetermined response line intercepting
at 100 mm Hg rather than 90 mm Hg diastolic, in view of the fact that blood pressure tends to rise with age. The intercept for systolic blood pressure was not increased in the elderly. Another partition was made according to the severity of starting diastolic hypertension to allow an assessment of efficacy in each group: mild (90 to 104 mm Hg), moderate (not below 105 to 114 mm Hg), and severe (115 mm Hg or greater).

**Results**

**Quantitative Analysis**

Little change occurred in mean blood pressures during the run-in period, with a small decrease of 2/1 mm Hg. With the introduction of indapamide alone or with

**Table 1. Mean Blood Pressure Reduction during 3-month Treatment with Indapamide Alone (2.5 mg/day) Statistically Tested by a Two-way ANOVA and Tukey's Multiple Range Test**

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastolic:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X (mm Hg)</td>
<td>104.6</td>
<td>93.8</td>
<td>90.9</td>
<td>88.7</td>
</tr>
<tr>
<td>SD</td>
<td>9.1</td>
<td>10.1</td>
<td>9.5</td>
<td>9.2</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X (mm Hg)</td>
<td>177.8</td>
<td>160.3</td>
<td>154.6</td>
<td>151.8</td>
</tr>
<tr>
<td>SD</td>
<td>21.8</td>
<td>20.5</td>
<td>19.2</td>
<td>19.2</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05 compared with all previous visits, Tukey's multiple range test.
a beta blocker, however, mean pressures fell progressively over the 3-month treatment period from 178/105 to 152/89 and 178/105 to 155/91 mm Hg respectively (see Figure 1). Age did not alter the effectiveness of the drug on diastolic blood pressure; a fall of −15 mm Hg was noted for both age groups. Patients older than 65 years produced a greater fall in systolic blood pressure (−26 mm Hg) than younger patients (−22 mm Hg). Mean baseline systolic pressures were 14 mm Hg (8%) higher in the older patients, however.

Figure 2. Predetermined line intercepting at 90 mm Hg with ±10 mm Hg limits showing the classification of drug response.

Figure 3. Scattergram with all data points (n = 1092) relating initial diastolic blood pressure and fall in blood pressure after 3 months of treatment with indapamide alone (2.5 mg/day), with the predetermined response line drawn through 90 mm Hg and a slope of 1 with ±10 mm Hg limits.
EVALUATION OF ANTIHYPERTENSIVE AGENTS/Campbell et al.

Diastolic Pressure

% group

<90  90  91-100 (mmHg)

Ex  Go  Ac  Po

0 month  3 months

Systolic Pressure

% group

<140 140 141-150 (mmHg)

Ex  Go  Ac  Po

0 month  3 months

Analysis of Variance

Analysis of variance carried out on diastolic and systolic blood pressures in patients receiving indapamide only showed a statistically significant \( p < 0.01 \) improvement in both measurements over the course of treatment. Furthermore, using Tukey's multiple range test, it was possible to show that this improvement was present at each visit compared not only to entry but to each previous visit \( p < 0.05 \) (see Table 1).

Correlation Analysis

Regression analysis was carried out on the baseline blood pressure against change in pressure at each visit, and all analyses showed a highly significant relationship \( r = 0.6, p < 0.001 \). The results for indapamide-treated patients at Month 3 are presented in Table 3. The slopes of the regression lines were similar for diastolic and systolic blood pressure (0.638 and 0.536 respectively), with intercepts of the \( x \) axis of 80 and 130 mm Hg respectively. A trend toward increasing slopes and correlation coefficients (Figure 6) and decreasing intercepts was observed as treatment continued, indicating a progressive improvement in blood pressure (approximately +20% in the slopes and −17% in the intercepts between Months 1 and 3).

Similar slopes and intercept were found for patients younger than age 65 years and those 65 years and older at the end of 3 months, but for the older group, maximum values for the slope and correlation coefficient occurred more quickly, within 2 months.

Analysis of the results for patients receiving indapamide and a variety of beta blocking drugs gave similar results to those of indapamide alone (slopes of between 0.676 and 0.475 and mean intercepts of 84 and 127 mm Hg for diastolic and systolic blood pressures, respectively, at Month 3; Table 4).

The results of regression analysis of age against fall in blood pressure showed that there was a statistically significant relationship between age and diastolic blood pressure \( p < 0.01 \); however, the value of \( r^2 \) (0.003) indicated a predictive value of less than 1%, and the slope of 0.05 mm Hg/yr had little clinical significance.

Qualitative Analysis

A significant correlation between baseline and the fall in blood pressure allowed a qualitative analysis to be undertaken. Visual inspection of the 3-month scattergram (see Figure 3) in comparison with the ideal predetermined line indicated that the majority of patients were above or just below this line. It also allowed individual patients to be examined and showed that indapamide was an effective antihypertensive agent in all groups, but tended to be less active in those...
Figure 5. Histogram representations of changes in blood pressure into initial, mild, moderate, and severe groups after 3 months of treatment with indapamide alone, calculated from predetermined ideal response line.

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Age group (yr)</th>
<th>Months</th>
<th>Excellent</th>
<th>Good</th>
<th>Acceptable</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastolic</td>
<td>&lt; 65 (n = 721)</td>
<td>3</td>
<td>28</td>
<td>46</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>≥ 65 (n = 372)</td>
<td>3</td>
<td>28</td>
<td>41</td>
<td>23</td>
<td>8</td>
</tr>
<tr>
<td>Systolic</td>
<td>&lt; 65 (n = 721)</td>
<td>3</td>
<td>18</td>
<td>27</td>
<td>24</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>≥ 65 (n = 371)</td>
<td>3</td>
<td>8</td>
<td>14</td>
<td>22</td>
<td>56</td>
</tr>
</tbody>
</table>

with severe disease with diastolic pressure greater than 130 mm Hg. More precise interpretation of the data, however, was obtained by examination of the histograms based on the four zones of the scattergram.

The results for patients receiving indapamide only (see Figure 4) showed an overall movement from poor to good control for both diastolic and systolic pressures. Normalization to 90 mm Hg or less was achieved in 73% of patients and only 6% were still above 100 mm Hg compared to 50% before treatment. The effect on systolic blood pressure was less pronounced, but the percentage of patients in whom this pressure was greater than 150 mm Hg fell from 88 to 40% within the 3 months. Similar results were found
EVALUATION OF ANTIHYPERTENSIVE AGENTS/Campbell et al.

**Table 3. Regression Analysis of Baseline vs Change in Blood Pressure after 3-month Treatment with Indapamide Alone (n = 1092)**

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Intercept on the x axis (mm Hg)</th>
<th>Slope</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastolic</td>
<td>80</td>
<td>0.638</td>
<td>0.558</td>
</tr>
<tr>
<td>Systolic</td>
<td>130</td>
<td>0.536</td>
<td>0.579</td>
</tr>
</tbody>
</table>

with the indapamide–beta blocker combination.

When the groups were analyzed for the effectiveness of the drug on diastolic pressure, in subdivisions mild (90–105 mm Hg), moderate (105–115 mm Hg), and severe (≥115 mm Hg) hypertension, diastolic pressure decreased to 90 mm Hg or below in 84%, 67%, and 49% respectively of patients over age 65 years. Indapamide was equally effective on diastolic pressure (see Table 2), but slightly less so on the more resistant systolic blood pressure, with 22% normalized to 140 mm Hg or less, compared to 45% for the younger group.

**Table 4. Regression Analysis of Baseline vs Change in Blood Pressure after 3-month Treatment with Indapamide and Beta Blocker Combination (n = 365)**

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Intercept on the x axis (mm Hg)</th>
<th>Slope</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastolic</td>
<td>84</td>
<td>0.676</td>
<td>0.568</td>
</tr>
<tr>
<td>Systolic</td>
<td>127</td>
<td>0.475</td>
<td>0.576</td>
</tr>
</tbody>
</table>

**Side Effects**

Adverse reactions were particularly rare in this study, and dropouts among those taking indapamide alone were fewer than 2%. These were not taken into account in the analysis.

**Discussion**

Most antihypertensive agents, alone or in combination, will produce a significant reduction in blood pressure in time. What is frequently not known is to what extent this reduction occurs in the general hypertensive population and in which particular patients. Will there be a similar percentage reduction in all degrees of the disease? Will the drug be equally active in elderly patients, male or female, Caucasians, Jamaicans, those with high or low circulating renin, and so on? Small, well-controlled, comparative studies may answer some of these questions, but results may only reflect the particular subjects under test rather than the population as a whole, in whom the therapy will be used. Larger multicenter studies, although more difficult to organize, are therefore preferable.

In this study of more than 1000 patients, it was possible to take a fresh approach to the evaluation of antihypertensive drugs that allowed a more flexible method of assessing the data and provided greater information on the use of a particular agent in concise, quantitative statistical or qualitative graphic representations. Scattergrams, as described here, are not only visually acceptable, providing information on the
range of pretreatment and final pressures, but also show how individuals responded, without losing the reader in a morass of statistical calculations. The use of an ideal predetermined response line, or bench mark, that could be altered to suit the patients under investigation, for example, 90 mm Hg for young hypertensives and 100 mm Hg for elderly patients,

provided a more objective end point for testing the activity of the drug in all degrees of hypertension. The use of tolerance limits around this line also allowed gradings of effectiveness for the whole population or its subdivisions to be calculated and represented in simple histograms. The size of this population study made it possible to stratify the data without loss of power in the analysis and to obtain comparable information on subgroups with mild, moderate, and severe disease; the elderly; and patients receiving combination therapy.

Although this form of analysis is ideally suited to large sample sizes of greater than 100, there is no reason such an approach cannot be used for smaller populations, providing that the range of starting pressures is large and that the power of the study is sufficiently high to detect significant differences between treatments. A review of antihypertensive drug studies published in the British Journal of Clinical Pharmacology in one year showed that, on average, only 19 patients were used per study. Clearly, this number is insufficient to attempt the type of analysis reported here. Small studies, although well-controlled, can lead to erroneous and conflicting conclusions, as well as to loss of essential population statistics; therefore well-designed large trials are generally preferable.

The basis for this type of analysis is the assumption that any antihypertensive agent will lower blood pressure to an extent that is proportional to the initial starting blood pressure, provided that the dosage is titrated when necessary. It was suggested, however, that this effect is not common to all drugs and that normalization is dependent on the agent’s mode of action and may be peculiar to calcium antagonists, which act only when a functional abnormality is present in the smooth muscle cell. This does not seem to be the case, and one review has shown that several drugs of widely differing modes of action and combinations of therapies possess this activity. Not all drugs in this review were the same, however; for example, metazolone and propranolol may not exhibit this linear regression. Similarly, the slopes and intercepts vary widely from one drug to another. This method of data presentation therefore allows each agent to be compared with the profiles of others in a way not usually considered. The number of patients falling into each of the qualitative categories in each subset of severity of hypertension can be compared directly with other drugs.

Individual variations in response to therapy can be observed and corrected for differences in compliance, blood level, and dosages. Although in this example indapamide was able to reduce blood pressure in all groups at a fixed dosage, this may not be true of other agents.

The equation of the computed regression line for each drug provides direct information on its overall potency or ability to lower blood pressure. If, for example, the line intercepts the initial blood pressure line above 90 mm Hg, it suggests that in the general population an agent will fail to bring the diastolic pressure to below this figure, and patients who start with initial pressures less than this intercept are unlikely to respond. In our study, the intercept for indapamide on the diastolic pressure axis was 90 mm Hg, suggesting that the drug has the ability to lower pressures to this extent. The slope of this line indicated the ability of the drug to lower blood pressure in more severely hypertensive patients. An ideal drug will have a slope of 1; the further this value is away from 1, the less the likelihood of effective treatment at higher initial blood pressures. Wilson and Schumacher showed that for 10 drugs in an average of 39 patients, where the dose was titrated, the intercept was 94 mm Hg and the slope was 0.49. This compared with the 1092 patients treated with a fixed dose of indapamide where an intercept of 80 mm Hg and a slope of 0.56 was found.

Much of this discussion has focused on measuring changes in diastolic blood pressure, since previous studies either did not investigate systolic blood pressure or found that the fall in systolic pressure was unrelated to the baseline level. Indapamide, however, appears to reduce systolic blood pressure in a similar fashion to that of diastolic blood pressure, and the importance of systolic pressures, particularly in the elderly who have high-resistance vessels, should not be overlooked. It remains to be seen if other drugs share this activity with indapamide.

The advantages of this assessment are evident, but equally there are disadvantages and possible criticisms. First, the design of our study might be criticized since it was not placebo-controlled or double-blind. Several other groups have already shown the drug to be significantly more active than placebo, but this was not our aim. A large number of centers recruiting average five patients is, at first sight, a possible basis for criticism, but in fact closely reflects the patient population as seen by the general practitioner, and any differences in technique, for example, measuring blood pressure, will produce random rather than systematic errors in the analysis.

Perhaps the major reason investigators have not used this approach in the past is out of fear that it contravenes accepted statistical procedures. Regression analysis on data that are not independent, such as starting and finishing blood pressures, is not acceptable if simple statements and conclusions on the correlation are drawn. In our approach, it was assumed before analysis that a correlation existed but that regression would differ from one drug to another. It is the differences between these regressions, not the fact that the regressions are found, that are of importance in this form of analysis and are used to compare the overall activity of each therapy.

The phenomenon of regression to the mean must also be considered. This is based on the observation
that subjects who have high blood pressure during an initial screen are more likely to show a decrease than an increase in blood pressure on subsequent measurements, without any intervening therapy. Similar considerations hold for any high or low measurements, including batting averages, dice throwing, or examination results, and create a statistical artifact due to the measurement being in the tail of the distribution curve. Methods have been reported to minimize this effect in parallel, placebo, and uncontrolled studies. The problem is of particular importance when the screening blood pressure is used also as a baseline measurement for comparison with pressure obtained later, but becomes a significant artifact only when the correlation between the initial and final measurements is small.

In this study, this effect was minimized since baseline measurements were obtained during a second visit after an interim period of 4 weeks from the initial screening. This is thought to be a better technique than taking several measurements on the same entry day and using the last as an initial value. The observations that indapamide continued to exert an antihypertensive action throughout the 3 months and that the correlation coefficient increased over this period also suggested that the effect of regression to the mean was minimal. Although this effect is always present in uncontrolled studies, it can be taken into account in the design and interpretation of the study and should not dissuade the investigator from using this approach.

This procedure may have wider applications and is not specific to the evaluation of antihypertensive drugs. It can, in principle, be used for any therapy that alters reproducibly measured abnormal variables that reflect the disease state and for which there is a clearly defined end point and an achievable normal level; two such therapeutic areas are obesity and diabetes. It has been possible to show that the weight loss achieved with the antiobesity agent fenfluramine over 6 months, is significantly related to initial weight ($r = 0.550$, $p < 0.001$, 48 patients), and the hypoglycemic activity of the sulphonylurea gliclazide is directly correlated with initial blood sugar levels after treatment for 3 months ($r = 0.462$, $p < 0.001$, 170 patients; D. B. Campbell, unpublished data).

In conclusion, it appears that for many drugs there is a relationship between the patient's initial abnormality and the change the therapy elicits. This relationship can be used to examine the activity and potency of drugs and to compare indirectly their profiles in objective and easily understandable procedures. It is particularly suitable for large populations, but can be used for smaller groups provided there is a range of baseline blood pressures. The possibility of regression to the mean must be taken into account in the design of the study and, if necessary, its contribution to the results can be removed by correction. Even if this method is not used, it appears prudent in antihypertensive studies to report the magnitude of absolute blood pressure reductions in relation to the initial pressures.

Acknowledgments

We would like to thank all of the physicians who took part in this study, Drs. Carey Bowker and Martin Wheeley for the design conduct of the trial, and Dr. Ken MacRae for his expert statistical guidance. We would also like to thank Mrs. Nasim Manuel for the efficient compilation of this manuscript.

References

1. Veterans Administration Cooperative Study Group on Antihypertensive Agents: effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressures averaging 90 through 114 mm Hg. JAMA 1970;213:1143-1152
A fresh approach to the evaluation of antihypertensive agents.
D B Campbell, S Lowe, D Taylor, P Turner and N Walsh

Hypertension. 1985;7:II143
doi: 10.1161/01.HYP.7.6_Pt_2.II143

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1985 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/7/6_Pt_2/II143

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/