Prevalence of Drug Resistant Hypertension

MICHAEL H. ALDERMAN, NANCY BUDNER, HILLEL COHEN, BERNARD LAMPORT, AND WEE LOCK OOI

SUMMARY Hypertension patients (1781), drawn from seven large employee groups in and around New York City, were studied to determine the prevalence of resistant hypertension among them. The blood pressure criteria for resistance (potential resistance) were failure to reach and maintain a blood pressure < 160/95 mm Hg on two separate occasions during at least 1 year of treatment. Confirmed resistance required that during the same period of follow-up, in which at least two antihypertensive agents had been prescribed simultaneously, blood pressure control had not been achieved. Potential resistance during 1 year of treatment was found in 75 patients (4.2%), and confirmed resistance for the same period was found in 52 patients (2.9%). Diastolic resistance was far more common than systolic; the systolic/diastolic resistance was the rarest of all. Of the 52 patients with confirmed resistance for the first year, 33 achieved control in subsequent years. In sum, true resistance as defined by rigorous criteria pertaining to the hypotensive effects of pharmacological intervention in the general population is exceedingly rare. (Hypertension 11 [Suppl II]: II-71-II-75, 1988)

KEY WORDS • hypertension • drug resistance • prevalence

In 1978, Gifford and Tarazi1 wrote that hypertension truly resistant to antihypertensive drug therapy was a disappearing phenomenon in an era of explosive pharmacological response to the need for hypotensive agents. To this date, however, the exact magnitude of the problem remains ill defined.

We reviewed 37 articles dealing with the problem of resistant hypertension that appeared in the English language literature from 1975 to 1985. Of these, 151-15 had a quantitative definition of the condition, and only two3-4 addressed the issue of prevalence by identifying a denominator from which resistant cases were drawn. The first, a Swedish study reported in 1977,2 found 20 of 589 (3%) patients with persistent blood pressure > 200/100 mm Hg after 2 years of “adequate” therapy. All were patients drawn from a hypertension clinic. The second, by Swales and colleagues3 of the University of Leicester in England, reviewed the total 1974-to-1981 experience of the hypertension clinic. Of 957 presumably self-selected patients, 126 (13%) failed to reduce diastolic blood pressure to 100 mm Hg over some unspecified time. The authors indicated that in these severely ill patients, failure to achieve control for even a short time was hazardous. The 126 so-called resistant patients were then allocated to subsequent therapy with either diazoxide, minoxidil, captopril, or quadruple therapy with prazosin and hydralazine, a B-blocker, and a diuretic. Within weeks, almost all were controlled, and thus, it is questionable whether these patients should be classified as having resistant hypertension.

To provide a basis upon which to estimate the maximum prevalence of drug resistant hypertension in a general community, we have examined the experience of a hypertensive cohort drawn from a general working population in and around New York City.16 A precise definition of resistance that includes blood pressure, therapy, and time was constructed and rigorously applied to the whole hypertensive population. We now report the prevalence of hypertension in this defined general population.

Patients and Methods

A worksite-based hypertension control program serves the employees of seven large employee groups in and around New York City.16 Workplace screening identified all hypertensive patients. Of these, 65 to 80% elected an on-site treatment program. A systematic protocol for evaluation and therapy, including a stepwise incremental drug regimen, guides the treatment of some 3600 employee patients now in care at 23 locations.17 The present report analyzes the experience of those 1781 patients who entered the program after 1981 and who had the opportunity of at least 1 year follow-up. Thus, patients entering within the past year or those (6% annually) who left the program before 1
To be eligible for study, patients had to be followed for at least 1 year. Potential resistance was defined on the basis of blood pressure criteria alone. Confirmed resistance required that at least two antihypertensive agents had been prescribed simultaneously. The blood pressure criteria for potential resistance (Figure 1) were failure to reach and maintain, on two separate occasions, a blood pressure < 160/95 mm Hg. On each occasion, the blood pressure value was the average of the last two of three pressures taken. A significant decline without achievement of control was also grounds for removing a patient from the resistant category. A significant decline was arbitrarily defined as a fall of 10% diastolic and 15% systolic. Under these conditions, a person with an initial diastolic blood pressure of 120 mm Hg that fell to a minimum of 105 mm Hg would still not be classified as resistant. In fact, however, only 18 patients were included in the significant decline group, and of these, only one had a diastolic blood pressure consistently > 100 mm Hg.

**Results**

Figure 2 depicts the experience of the total group including complete and incomplete evaluations. As can be seen, the prevalence of potential resistance is substantially different in the two groups, with 2.7% of the complete and 10.3% of the incomplete group meet-
The prevalence of confirmed resistance in the two groups was 1.7 and 8.2%, respectively.

The substantial and significant difference in observed outcome is reflected in the characteristics of the two groups. The complete evaluation group was younger (45 vs 55 years old, \( p < 0.005 \)) but did not differ in sex, race, and marital status. In terms of clinical status, however, the incomplete evaluation group had substantially more intermittent claudication and greater alcohol consumption (Table 1). Left ventricular hypertrophy and retinopathy, reflected by KW class 3 and 4, were far more prevalent among the incomplete evaluation patients. Likewise, their blood pressure, body mass index, blood sugar, and cholesterol were also higher.

In sum, then, patients who by and large did not tolerate a 4-week period of drug withdrawal were older, had more evidence of cardiovascular disease or the propensity for it, and had a higher likelihood of drug resistance.

The type of resistance observed in the total group is depicted in Figure 3. Of those 75 (4.2%) who met the criteria for potential resistance, only 52 (2.9%) used two drugs and were therefore categorized as confirmed resistant. It can be seen that diastolic resistance, although less hardy than systolic, was far more common. Resistance in both components of pressure measurement was the rarest of all.

When the confirmed resistant group is compared

<table>
<thead>
<tr>
<th>TABLE 1. Clinical Characteristics of Complete and Incomplete Evaluated Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete evaluation (( n = 1431 ))</td>
</tr>
<tr>
<td>Age ( \geq 55 )</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Angina</td>
</tr>
<tr>
<td>Int claudication</td>
</tr>
<tr>
<td>Dyspnea</td>
</tr>
<tr>
<td>Mod/Heavy alcohol</td>
</tr>
<tr>
<td>Fundi 3+</td>
</tr>
<tr>
<td>LVH/ECG</td>
</tr>
<tr>
<td>Blood pressure Uncontrolled at entry</td>
</tr>
<tr>
<td>( n = 582 )</td>
</tr>
<tr>
<td>SBP</td>
</tr>
<tr>
<td>DBP</td>
</tr>
<tr>
<td>Controlled at entry</td>
</tr>
<tr>
<td>SBP</td>
</tr>
<tr>
<td>DBP</td>
</tr>
<tr>
<td>Mean BMI</td>
</tr>
<tr>
<td>Mean FBS</td>
</tr>
<tr>
<td>Mean Chol</td>
</tr>
</tbody>
</table>

BMI = body mass index; FBS = fasting blood sugar; Chol = cholesterol.
\(* p < 0.05, \dagger p < 0.01, \ddagger p < 0.005.\)

\( \ddagger \) Received medications before entering the program.

**FIGURE 3.** Confirmed drug resistant hypertension among patients with 1 year follow-up.
with the controlled group, age and race did not vary, whereas maleness was strongly associated with resistance (Table 2). Cardiovascular symptoms and habits, including smoking, did not differ between the two groups. There were, however, significant differences between the two groups in such relevant areas as blood pressure, body mass index, retinopathy, fasting blood sugar, and cholesterol, with tendency for the resistant group to have a higher prevalence of left ventricular hypertrophy, although not statistically significant. In sum, therefore, it would appear that at entry the resistant patients had a tendency to a greater risk of cardiovascular disease than those who subsequently became controlled.

The most telling distinction between the resistant and controlled groups, however, lay in compliance as reflected by adherence to drug prescription. Of those patients who achieved control, 43% admitted to missing some of the drugs on at least one visit. The comparable figure for the resistant group was 60%, and this differed significantly (p < 0.005) from the controlled group.

The potential impact of compliance upon these findings is further reflected by the experience of our resistant group after the first year. Of the 52 who were classified as having confirmed resistance for the first year, 33 achieved blood pressure control in subsequent years. Of the remaining 19, 14 admitted to questioning by their nurse therapists that they at least intermittently did not take their medication as prescribed. In the final analysis, then, of 1781 patients drawn from this employed New York City population, there were five patients (0.3%) who took at least two medications, presumably faithfully, and yet ultimately failed to achieve a satisfactory response. These five were young (24–56 years old), had higher entry diastolic blood pressure (106 vs 101 mm Hg), and, most strikingly, were all black. None had abdominal bruit, nor had grade III or IV retinopathy, nor were classified as high renin.

**Discussion**

While the persistence of uncontrolled hypertension among treated patients continues to plague those who seek to solve the public health problem of high blood pressure, the data here would suggest that the most likely explanation for the problem is almost certainly not pharmacological unresponsiveness. In the program examined here, in which a systematic therapeutic regimen was provided in a setting designed to remove impediments to the receipt of care and in which a variety of social supports were in place to encourage compliance, failure to control or significantly reduce pressure was very rare. In this program, cost was removed from the patient-therapist encounter, and drugs were provided free and delivered to the patient's home. Under these circumstances, the net result was that no more than 3% of all patients were refractory to treatment for even 1 year, and, with longer follow-up and taking into account noncompliance, the drug resistant hypertension might virtually disappear—in essence, yielding a resistance-free population.

In previous reports, no particular effort was made to assemble and define a population for study. Although these data did not derive from a prospective design specifically established to address the question of drug resistance, the manner of this study does permit a fair assessment of the question. Patients were sought in a general free-living population and more than two thirds of all identified hypertensive patients enrolled in therapy. Thus, we believe that the group evaluated was highly representative of the whole community, and therefore, these findings can be safely extrapolated to other general populations.

A well-defined treatment schedule was the keystone of the therapeutic approach of this worksite program. Treatment targets were predetermined and specific. Under these circumstances, failure to prescribe adequately was probably an uncommon event. Moreover, in this program, most patients (80%) at any given time were under control. Of the 20% with blood pressure >160/95 mm Hg at any given time, only 4.2% had failed to control their pressure and could be classified as potentially uncontrolled. This small group is the maximum size of a difficult-to-treat group that can be expected under optimal therapeutic circumstances. This group was then further reduced to 2.9% when inadequately treated patients were excluded. Referral centers, which draw from large population areas, may appear to encounter larger numbers of potentially resistant patients, but this likely reflects selection bias or unsatisfactory prior therapy (or both).
The cause of the resistance noted here cannot be determined from the data available in this study. We cannot even unequivocally establish whether the pills prescribed were actually taken. Clearly, nonadherence figured prominently in the data presented, and whether it might ultimately explain every single treatment failure can only be determined through clinical study. Alternately, a secondary cause of hypertension, such as pheochromocytoma, renal artery stenosis, or a drug interaction that blunted antihypertensive effectiveness, must be considered as a potential cause of truly resistant hypertension. In this regard, it is of note that the hard core of five persistently resistant patients had no evidence to suggest the presence of any of these conditions. Careful study of this handful of patients may shed new light on the pathophysiology of hypertension.

It is clear from this experience that the identification of this handful of resistant hypertensive patients should be based upon rigid application of specific criteria. The criteria used here were arbitrary but seemed to effectively segregate two groups of patients. Even then, however, a further clinical review of the course of the 2.9% confirmed resistant patients through the first year diminished that modest number nearly to zero. Our pharmacological capability would seem to overwhelm the fragility of elevated pressure.

What then can finally be said about the prevalence of resistant hypertension? It may exist but is clearly rare and should in no way be viewed as a serious impediment to the widespread control of high blood pressure. These findings confirm what Gifford and Tarazi1 presumed almost a decade ago! The tools are not the result of a technological shortfall. Rather, a secondary cause of hypertension, such as pheochromocytoma, renal artery stenosis, or a drug interaction that blunted antihypertensive effectiveness, must be considered as a potential cause of truly resistant hypertension. In this regard, it is of note that the hard core of five persistently resistant patients had no evidence to suggest the presence of any of these conditions. Careful study of this handful of patients may shed new light on the pathophysiology of hypertension.

It is clear from this experience that the identification of this handful of resistant hypertensive patients should be based upon rigid application of specific criteria. The criteria used here were arbitrary but seemed to effectively segregate two groups of patients. Even then, however, a further clinical review of the course of the 2.9% confirmed resistant patients through the first year diminished that modest number nearly to zero. Our pharmacological capability would seem to overwhelm the fragility of elevated pressure.

What then can finally be said about the prevalence of resistant hypertension? It may exist but is clearly rare and should in no way be viewed as a serious impediment to the widespread control of high blood pressure. These findings confirm what Gifford and Tarazi1 presumed almost a decade ago! The tools are available to contain hypertension in virtually every patient. Uncontrolled hypertension is almost invariably not the result of a technological shortfall. Rather, when patients continue to have elevated blood pressure, despite aggressive application of drugs, the physician should expect to find its explanation in the behavior of one of the two parties to the therapeutic encounter.

References
Prevalence of drug resistant hypertension.
M H Alderman, N Budner, H Cohen, B Lamport and W L Ooi

*Hypertension*. 1988;11:II71
doi: 10.1161/01.HYP.11.3_Pt_2.II71

*Hypertension* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1988 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/11/3_Pt_2/II71

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/