Benefits of adherence to anti-hypertensive drug therapy

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Long-term adherence or compliance with anti-hypertensive drug therapy is poor. It has been estimated that within the first year of treatment 16–50% of hypertensives discontinue their anti-hypertensive medications. Even among those who remain on therapy long term, missed medication doses are common. Epidemiological studies have shown that drug-treated hypertensives have higher blood pressures than age-, gender- and body mass index-matched normotensives. In addition, drug-treated hypertensive men and women who achieve blood pressure normalization are less likely to die over a 9-5-year period than those whose blood pressure remains elevated while taking anti-hypertensive drugs. Thus, one reason for less than optimal reduction of blood pressure-related cardiovascular-renal risk in drug-treated hypertensives is inadequate blood pressure lowering. Quantifiable excess risk has been documented even in the short term (<1 year) after interruption or discontinuation of anti-hypertensive medications as total healthcare costs are higher, mostly because of higher hospitalization rates.

Data from the Treatment of Mild Hypertension Study (TOMHS) are relevant to long-term adherence to various anti-hypertensive drug monotherapies. At 48 months, 82.5% and 77.8% of participants remained on amlodipine and acebutolol, respectively (both \( P < 0.01 \) compared with placebo). However, only 67.5%, 66.1% and 68.1%, respectively, of chlorthalidone, doxazosin and enalapril participants remained on these drugs as monotherapy at 48 months. Differential adherence to long-term anti-hypertensive drug therapy could translate into a greater risk of blood pressure-related complications and higher overall healthcare expenditures. Strategies to minimize the deleterious impact of therapeutic non-adherence with anti-hypertensive medications as well as the clinical and cost implications of the TOMHS data will be discussed.

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Introduction

The devastating clinical sequelae attributable to hypertension are well documented and include both cardiovascular-renal diseases and premature mortality[1,2]. Moreover, the risk of excessive morbidity and mortality are present even among persons with so-called ‘mild’ hypertension. Nevertheless, it has been documented that long-term anti-hypertensive drug therapy lowers the risk for blood pressure-related clinical events, including premature mortality[3,4]. Specifically, anti-hypertensive drug therapy has been shown to reduce the risk of stroke, myocardial infarction (MI), progression of hypertension to more severe levels and congestive heart failure[5,4]. However, a major obstacle to obtaining the aforementioned risk reductions is the pervasive problem of non-compliance with prescribed anti-hypertensive drug therapy.

In newly diagnosed hypertensives, between 16% and 50% of persons will discontinue their anti-hypertensive medication during the first year[6-9]. Even among those who remain on therapy, a substantial proportion will routinely miss medication doses[10]. Thus, the problem of therapeutic non-compliance can be viewed as having at least two dimensions. The first dimension relates to the long-term task of keeping patients on their prescribed medications, while the second dimension concerns minimizing missed medication doses among persons remaining on long-term drug therapy.

What factors influence adherence?

Table 1 displays a list of factors known to influence adherence to anti-hypertensive drug therapy. Women are more likely than men to adhere to an anti-hypertensive drug regimen as well as to achieve blood pressure control when taking blood pressure-lowering medication[8,10]. Moreover, men are more likely to be unaware of their hypertension than women and even when men are aware of their hypertension they are less likely than women to be receiving anti-hypertensive medication[11]. Possibly to the surprise of some, younger age has also been associated with poorer adherence to blood
pressure-lowering medication\textsuperscript{[12,13]}, although some studies have not confirmed this observation. Interestingly, older patients tend to discontinue treatment because of adverse effects, whereas younger patients quit their medications because of improvement under therapy\textsuperscript{[14]}. Importantly, physicians fare poorly when they attempt to subjectively estimate therapeutic compliance\textsuperscript{[15]}.

Side effects that are perceived as secondary to anti-hypertensive medication have correlated with non-adherence to anti-hypertensive drug regimens in several previous studies\textsuperscript{[10,16,17]}. Thus, the magnitude of expected medication side effects should be an important consideration when prescribing anti-hypertensive drug therapy. It can be difficult to know, at least with any degree of confidence, if side effects occurring during anti-hypertensive drug therapy are actually caused by the prescribed medication(s) because there is overlap between clinical symptoms attributable to hypertension and drug-induced side effects. In addition, perceived side effects are more likely to occur at the beginning of therapy and tend to decrease in frequency over time, probably because of psychological rather than pharmacological factors\textsuperscript{[18]}.

Headaches can occur either as a consequence of hypertension or as a side effect of certain anti-hypertensive medications, particularly those belonging to the vasodilator class. In the Treatment of Mild Hypertension Study (TOMHS) (average pre-treatment blood pressure 140/91 mmHg), drug-treated hypertensives had fewer headaches than hypertensives taking placebo, even though both groups had average blood pressure levels within the normal range (<140/90 mmHg)\textsuperscript{[19]}. This finding suggests that even patients with stage I or 'mild' hypertension are symptomatic and that low to moderate doses of anti-hypertensive drug therapy can lessen the burden of these symptoms.

The widespread misperception, held by both patients and physicians, that hypertensives are infrequently symptomatic probably contributes to therapeutic non-compliance, particularly among drug-treated hypertensives who have elevated blood pressure. In such patients, blood pressure-related symptoms (i.e. headache, poor exercise tolerance, fatigue) are often blamed on their anti-hypertensive medications. Thus, the patient may be reluctant to take the necessary higher doses of medication or additional medications to achieve blood pressure control, because they have mistakenly blamed their blood pressure-related symptoms on their anti-hypertensive medications.

### Does adherence influence blood pressure control or risk of adverse clinical events?

At least one way that non-compliance to anti-hypertensive drug therapy influences patient outcomes has been through worsened blood pressure control. Indeed, a substantial body of data has accrued regarding the effect of adherence to anti-hypertensive medication on blood pressure control. Black and coworkers\textsuperscript{[20]} reported data from the Systolic Hypertension in the Elderly Program (SHEP) pilot study showing that >80% compliance, as assessed by pill count, was associated with a greater probability of achieving target systolic blood pressure reductions both in the active (82.8% vs 61.5%) and placebo (34.6% vs 16.7%) treatment groups. The finding of a relationship between systolic blood pressure response and therapeutic compliance in the placebo group suggests that individual attributes positively associated with adherence to drug therapy independently contribute to blood pressure lowering. In this study men and women were equally compliant. A study by Nelson and colleagues\textsuperscript{[10]} also documented a positive correlation between diastolic blood pressure control and adherence to drug therapy in a relatively poor urban sample of hypertensive patients. In addition, 54% of patients deemed compliant, compared with 29% of non-compliant patients, reported missing no medication doses during the previous 4 weeks. Similarly, Hershey and coworkers\textsuperscript{[21]} found that hypertensive patients attending a university-based clinic, who reported total adherence to their regimen of blood pressure medications, achieved blood pressure control more often than those reporting less compliance (75% vs 53%, \(P<0.01\)).

Recently reported data\textsuperscript{[22]} from a hypertensive Medicaid population found that therapeutic non-compliance was associated with higher total healthcare costs. In this study, 86% of newly initiated anti-hypertensive drug therapy was interrupted or discontinued during the first year, resulting in total medical costs that were US$873/patient higher during that same year compared with hypertensives without documented non-compliance. The increased costs were primarily due to higher inpatient hospital expenditures totalling US$637/patient. Thus, in aggregate, these data suggest a link between the level of blood pressure control and compliance with anti-hypertensive drug therapy, as well as an immediate correlation of therapeutic non-compliance with increased healthcare expenditure.
What is the relationship of blood pressure control to adverse clinical outcomes?

In the United States sequential national surveys have shown that 'hypertension awareness' treatment and blood pressure control have improved steadily over the last several decades. Nevertheless, the absolute proportion of hypertensives who had achieved blood pressure normalization during the most recent National Health and Nutrition Survey III (NHANES III) during 1988–1991 was quite low. Only 21% of free-living hypertensives in the United States achieved a blood pressure level of <140/90 mmHg, although a more impressive 55% had blood pressure levels <160/95 mmHg. The NHANES I Epidemiological Follow-Up Study (Table 2) found an 82% and 97% higher 9-year age- and smoking-adjusted risk of mortality in drug-treated hypertensive white men and women, respectively, who had not achieved blood pressure control (<160/95 mmHg), compared with same gender normotensives. On the other hand, excess mortality among drug-treated hypertensives with 'controlled' hypertension (<160/95 mmHg) was somewhat less being only 36% and 30% higher in white men and women, respectively, compared with same gender normotensives.

A major reason for the inability to achieve a mortality risk in drug-treated hypertensives comparable with that in normotensives has been the problem in persistent blood pressure elevations despite pharmacotherapy. Observations made by Flack and Wistl are also consistent with this line of reasoning. They documented higher blood pressures in middle-aged African-American hypertensives than in age-, body mass index- and gender-matched normotensives (men 139/88 vs 132/83 mmHg; women 139/86 vs 129/79 mmHg). Stated another way, these hypertensives never achieved the lower blood pressure levels of same gender normotensives who were the same age and of similar body size. Thus, poor blood pressure control, which occurs in no small consequence because of poor adherence to long-term anti-hypertensive drug therapy, plays a substantial role in the development of increased risk of excess mortality experienced by drug-treated hypertensive men and women.

### The Treatment of Mild Hypertension Study (TOMHS)

TOMHS was a multicentre, randomized, placebo-controlled clinical trial involving 902 men and women aged 45–69 years, most of whom had so-called 'mild' or Stage I hypertension. The range of pre-treatment diastolic blood pressure was 90–99 mmHg among those not taking medication at baseline (39–1%), while diastolic blood pressure ranged between 85 and 99 mmHg among the larger group (60–9%) who were taking medication at baseline. Blood pressure averaged 140/91 mmHg at randomization. Participants were randomized to lifestyle modification (weight loss, salt and alcohol restriction, physical activity increase) or placebo plus one of five active drug therapies. Active drug treatments included chlorthalidone (15 mg . day$^{-1}$), acebutolol (400 mg . day$^{-1}$), amloidipine (5 mg . day$^{-1}$) enalapril (5 mg . day$^{-1}$) and doxazosin (2 mg . day$^{-1}$). Analyses relating to hard clinical events, such as MI and stroke, were not drug specific but were aggregate contrasts of all active drug groups combined (drug plus lifestyle modification) compared with placebo (lifestyle modification only). Follow-up averaged 4.4 years.

Blood pressure was lowered an average of $-15.9/-12.3$ mmHg and $-9.1/-8.6$ mmHg in the combined drug and placebo treatment groups, respectively. The between-group difference of 6.8/3.7 mmHg was highly significant both for systolic and diastolic blood pressure ($P<0.0001$). After 48 months of follow-up, blood pressure averaged 126.7/79.4 mmHg and 132.6/81.9 mmHg in the combined drug and placebo treatment groups, respectively. Thus, both groups attained systolic and diastolic blood pressure levels that were within the 'normal' range (<140/90 mmHg). There was no difference in diastolic blood pressure lowering among the five drug groups. However, average systolic blood pressure lowering during follow-up was greater with chlorthalidone (−17 mmHg) compared with amloidipine (−15.6 mmHg), doxazosin (−14.2 mmHg) and enalapril (−14.7 mmHg). The average reduction in systolic blood pressure was significantly greater with acebutolol (−17.0 mmHg) compared with doxazosin (−14.2 mmHg) ($P<0.01$) and with chlorthalidone compared with doxazosin and enalapril ($P<0.01$). Furthermore, at 48 months all drug treatments, with the exception of enalapril, had significantly lowered blood pressure compared with placebo ($P<0.01$).

Table 3 displays long-term adherence data according to drug treatment group. Long-term adherence was defined as the proportion of participants randomized to each drug who remained on their initial treatment assignment (monotherapy) at 48 months. Only amloidipine (82.5%) and acebutolol (77.8%) demonstrated significantly greater long-term drug adherence than placebo (58.5%) (both contrasts, $P<0.01$). Further-
more, among the five drug groups, greater long-term adherence was documented for participants taking amlodipine compared with participants taking either chlorthalidone or doxazosin (P<0.01 for both contrasts).

Major coronary heart disease and cardiovascular disease events were 36% lower in the combined drug treatment group compared with the placebo group (4.49% vs 6.84%, P=0.15). When other clinical events were also considered, the event rate was 34% lower in the combined drug treatment group compared with the placebo group (11.08% vs 16.24%, P=0.03).

### Implications of the TOMHS data

The TOMHS study suggests that there are long-term differences in adherence to anti-hypertensive drug therapy in patients with mostly 'mild' or Stage I hypertension. Adherence to any drug therapy is, minimally, a result of the combined forces of blood pressure-lowering efficacy and patient tolerability of the prescribed drug. Patient tolerability will, to no small degree, relate to perceived side effects. Drugs that result in a high degree of therapeutic non-adherence can increase total healthcare costs, because patients taking these drugs will have a greater number of clinic visits triggered by perceived side effects. Conversely, drugs with greater long-term tolerability will minimize overall healthcare costs because fewer clinic visits for perceived medication side effects. Furthermore, Elliott et al.[29] performed an interesting analysis in a tertiary Hypertension Clinic of the costs associated with discontinuing 'preferred therapy' with diuretics and β-blockers (as recommended in the Fifth Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure [JNC-V]) and switching to alternative drug treatments. During the ensuing 12 months after the therapeutic switch was made, $1333 in total medical care costs were generated; these patients underwent two additional clinic visits (5.9% vs 4.1%; P<0.01) with much of the additional monetary expenditure going towards blood pressure monitoring and laboratory costs. Thus, in spite of the low acquisition costs of 'preferred' anti-hypertensive drug therapies, there is a sizable financial cost when patients (such as those experiencing side effects) are switched to alternative therapies. Drug acquisition costs must be, therefore, considered in the context of how they impact upon the non-drug portion of the healthcare expenditure equation.

Most anti-hypertensive drugs will ultimately lower blood pressure to a similar degree. In addition, when differences in blood pressure lowering occur, they can often be overcome by upward titration of a given medication. Thus, selection of initial anti-hypertensive monotherapy usually hinges on issues, such as co-existing medical conditions and side effects, rather than blood pressure-lowering efficacy. On the other hand, clinic visits often occur with upward titration of anti-hypertensive drugs, thus escalating the overall cost of medical care.

No authoritative expert panel has yet to recommend that blood pressure should be lowered well into the normal range (<140/90 mmHg) to achieve optimal attenuation of blood pressure-related morbidity and mortality. Clinical events. Yet, one interpretation of the TOMHS data would be that the lower the blood pressure the greater the reduction in risk for blood pressure-related sequelae.

Another important issue is related to drug half-lives. Missed medication doses are inevitable in many drug-treated hypertensives. Drugs with long intrinsic half-lives (see Table 4) provide both a more gradual onset of action (and probably more gradual onset of blood pressure lowering) and a slower offset of action. Thus, medication doses are missed there will be less loss of blood pressure control. Two TOMHS drugs with very long intrinsic half-lives were chlorthalidone and amlodipine.

### Table 3  Long-term (48-month) adherence to anti-hypertensive drug monotherapies in the Treatment of Mild Hypertension Study (TOMHS). Percentage values refer to the proportion of participants initially assigned to each drug group that remained on only that drug at 48 months

<table>
<thead>
<tr>
<th>Drug</th>
<th>On initial treatment (%)</th>
<th>Withdrawn (%)</th>
<th>Prescribed other blood pressure medication (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol*</td>
<td>77.8 (n=126)</td>
<td>7.9</td>
<td>14.3</td>
</tr>
<tr>
<td>Amlodipine*</td>
<td>82.5 (n=114)</td>
<td>6.1</td>
<td>11.4</td>
</tr>
<tr>
<td>Chlorthalidone*</td>
<td>67.5 (n=117)</td>
<td>14.5</td>
<td>17.9</td>
</tr>
<tr>
<td>Doxazosin*</td>
<td>66.1 (n=121)</td>
<td>12.4</td>
<td>21.5</td>
</tr>
<tr>
<td>Enalapril*</td>
<td>68.1 (n=119)</td>
<td>11.8</td>
<td>20.2</td>
</tr>
<tr>
<td>Placebo</td>
<td>58.5 (n=207)</td>
<td>8.7</td>
<td>32.9</td>
</tr>
</tbody>
</table>

*P<0.01 for placebo vs acebutolol and amlodipine; chlorthalidone and doxazosin vs amlodipine.

### Table 4  Relative length of drug half-lives, or duration of action of, among commonly used drug classes

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Chlorthalidone</th>
<th>&gt;Hydrochlorothiazide</th>
<th>ACE inhibitors</th>
<th>Quinapril</th>
<th>&gt;Captopril</th>
<th>Calcium antagonists</th>
<th>Amlodipine</th>
<th>&gt;Felodipine</th>
<th>Alpha; antagonists</th>
<th>Doxazosin</th>
<th>&gt;Terazosin</th>
<th>β-blockers</th>
<th>Atenolol</th>
<th>&gt;Propranolol</th>
</tr>
</thead>
</table>
| ACE=angiotensin converting enzyme.  

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Conclusion

Long-term adherence to anti-hypertensive drug therapy has proven benefits, even for persons with 'mild' or Stage I hypertension. Avoiding rapid reduction in blood pressure and using drugs with long intrinsic half-lives will provide maximum therapeutic coverage when medication doses are missed. To avoid over treating patients, unless the initial blood pressure elevation is severe, anti-hypertensive drugs should be titrated at no more frequent intervals than every 4–8 weeks. Finally, the therapeutic goal in most hypertensive patients should be gradual normalization of blood pressure (<140/90 mmHg).

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References