EXECUTIVE SUMMARIES ON HYPERTENSION II.
CHOICES OF INITIAL DRUG THERAPY

Norman M. Kaplan, M.D.

Professor of Internal Medicine, The University of Texas Southwestern Medical Center at Dallas, Dallas, Texas, USA

CONTENTS
Summary ............................................. 17
Introduction ....................................... 17
Recent Changes in Drug Therapy .................. 18
Recommendations and Guidelines ................. 19
JNC-VI Recommendations .......................... 19
Indications for Other Choices .................... 19
The Issue of CCB Safety .......................... 19
The Overall Plan of Therapy ...................... 20
The Need for Long-Acting Formulations .......... 20
Combination Therapy .............................. 21
Follow-up Care ..................................... 21
References .......................................... 22

Summary
Once the need for drug therapy has been determined, the JNC-6 report provides three pathways for the choice of therapy: for uncomplicated patients, a diuretic or β-blocker; for patients with diabetic nephropathy, isolated systolic hypertension, congestive heart failure or systolic dysfunction after myocardial infarction, specific drugs are compellingly indicated; for other conditions, certain drugs that provide favorable effects are recommended. Whatever drug is chosen, long-acting preparations that provide 24-h coverage with one daily dose are recommended.

Introduction
Once the diagnosis of hypertension is established and an appropriate trial of lifestyle modifications attempted, most patients will need antihypertensive drug therapy. The choices now available can easily be classified by their major mode of action (1) (Table I). The list is long and will continue to expand as more members of almost every class are introduced into the market.
Table I: Antihypertensive drugs available in the U.S.

<table>
<thead>
<tr>
<th>Volume depleters</th>
<th>Adrenergic inhibitors</th>
<th>Vasodilators</th>
<th>ACE inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>Guanadrel</td>
<td>Acetebutolol</td>
<td>Hydralazine</td>
</tr>
<tr>
<td>Indapamide</td>
<td>Guanethidene</td>
<td>Atenolol</td>
<td>Minoxidil</td>
</tr>
<tr>
<td>Metolazone</td>
<td>Reserpine</td>
<td>Betaxolol</td>
<td>Enalapril</td>
</tr>
<tr>
<td>Thiazides</td>
<td>Central</td>
<td>Bisoprolol</td>
<td>Captopril</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>Clonidine</td>
<td>Carteolol</td>
<td>Enalapril</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>Guanabenz</td>
<td>Metoprolol</td>
<td>Fosinopril</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Guanfacine</td>
<td>Nadolol</td>
<td>Lisinopril</td>
</tr>
<tr>
<td>Torasemide</td>
<td>Methyldopa</td>
<td>Penbutolol</td>
<td>Moexipril</td>
</tr>
<tr>
<td>K⁺ savers</td>
<td>α-Receptor</td>
<td>Pindolol</td>
<td>Quinapril</td>
</tr>
<tr>
<td>Amiloride</td>
<td>Doxazosin</td>
<td>Propranolol</td>
<td>Ramipril</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Prazosin</td>
<td>Nicardipine</td>
<td>Trandolapril</td>
</tr>
<tr>
<td>Triamterene</td>
<td>Terazosin</td>
<td>Timolol</td>
<td>All receptor blockers</td>
</tr>
</tbody>
</table>

Recent Changes in Drug Therapy

Over the past 10 years, major changes have occurred in the usage of various classes of antihypertensive drugs (Fig. 1). The changes shown in Figure 1 are from the usual retail providers in the U.S. In other countries with different cultural attitudes and pharmaceutical distribution systems, the changes may vary considerably from those in the U.S., but the general tendency has been away from the older, traditional choices toward the newer, more heavily promoted classes of angiotensin converting enzyme inhibitors (ACEIs) and calcium channel blockers (CCBs).

The intensive marketing of these newer classes (as well as the more recently introduced angiotensin II receptor blockers) almost certainly is a major reason for these profound changes in drug selection. However, many physicians believe that these newer classes provide additional benefits and patients often experience fewer side effects from them, so their increased use is not just a promotional payoff.

Fig. 1. Number of prescriptions in millions for antihypertensive drugs dispensed in retail channels in the U.S. from 1986 to 1996. (National Prescription Audit, Ambler, Pennsylvania: IMS, 1997.)
Recommendations and Guidelines

Various groups of hypertension experts have published guidelines for the treatment of hypertension. About half of these semi-official guidelines recommend that an agent from any of the 5 major classes – diuretics, β-blockers, α-blockers, ACEIs and CCBs – be chosen. The other half, including the U.S. Joint National Committee (JNC-VI), recommend the use of diuretics and β-blockers in the absence of compelling indications for the use of other agents.

As a member of the JNC-VI, I will describe their recommendations in greater detail but, at the same time, I recognize the rationale for other approaches.

JNC-VI Recommendations

As stated in the 1997 publication (2): “If there are no specific indications for another type of drug, a diuretic or β-blocker should be chosen because they remain the only classes of drugs that have been shown to reduce morbidity and mortality in long-term clinical trials. Multiple trials measuring these outcomes with the newer agents are in progress. If specific indications for other agents are present, the choice should be individualized, using the agent that most closely fits the patient’s need.” (Table II). Thus, the preference for a diuretic or β-blocker is predicated on the available evidence from multiple large, randomized, controlled trials performed over the last 25 years that used these agents and demonstrated significant reductions in cardiovascular morbidity and mortality (3) (Fig. 2).

Other expert committees have taken the evidence of protection shown in these trials using diuretics and β-blockers as being equally applicable to any drug that provides equal antihypertensive efficacy (4). There is little doubt that all 5 classes provide essentially equal antihypertensive efficacy in the overall population of hypertensive patients (5). However, as of now, there is little data from large controlled trials with the use of ACEIs, CCBs and other agents as to their ability to provide equal protection from cardiovascular morbidity and mortality in uncomplicated hypertensives. A large randomized, placebo-controlled trial with the CCB nitrendipine has been completed in elderly hypertensives, showing excellent protection against stroke and overall cardiovascular morbidity (6), and a large number of trials comparing the newer agents against the older drugs are in progress, so more evidence will be forthcoming.

In the meantime, I believe the overall algorithm of the JNC-VI report (Fig. 3) is a reasonable approach. If newer agents are shown to be better than diuretics or β-blockers, they obviously should be placed in the preferred position.

Indication for Other Choices

The JNC-VI algorithm (Fig. 3) indicates that specific choices other than diuretics or β-blockers may logically be chosen for various specific indications (Table II). In addition, the presence of a number of coexisting conditions mandates that certain drugs be avoided.

Table II indicates that only a few situations have been found wherein the choice of certain agents is “compelling.” Certainly, a patient who has survived an acute myocardial infarction should, in the absence of a definite contraindication, always be provided the proven benefits of a β-blocker and an ACEI.

Other specific conditions recommend the use of certain agents but with less compelling strength. An example is the use of an β-blocker in an elderly man with both hypertension and obstructive symptoms from benign prostatic hypertrophy. β-Blockers are clearly useful for the relief of prostatism and, at the same time, will effectively lower blood pressure, so the choice is logical (7).

The Issue of CCB Safety

A major controversy has risen over the safety of CCBs as I have described in a previous article for Drugs of Today’s Timely Topics in Medicine (8). Since that publication, additional evidence has documented both the probable hazards of short-acting CCBs (never indicated for the treatment of hypertension) and the safety of long-acting CCBs (approved for the treatment of hypertension). Although the ability of long-acting CCBs to provide cardiovascular protection remains poorly documented (as is true for ACEIs and AII receptor blockers), the evidence of their safety continues to mount. In particular, a prospective cohort study found that the use of short-acting CCBs was associated with almost a 4-fold increased risk of acute myocardial infarction, whereas the use of long-acting CCBs was associated with lower risk than seen with β-blockers (9).

In view of the increasing body of evidence attesting to their efficacy (6) and safety (9), I believe long-acting CCBs can be used without concern for the treatment of hypertension in those situations in which they are indicated (Table II).
### Table II: Considerations for individualizing antihypertensive drug therapy*

<table>
<thead>
<tr>
<th>Compelling indications, unless contraindicated</th>
<th>May have favorable effects on comorbid conditions</th>
<th>May have unfavorable effects on comorbid conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus with proteinuria ACEI</td>
<td>Angina, β-Blockers, CA</td>
<td>Bronchospastic disease, β-Blockers†</td>
</tr>
<tr>
<td>Heart failure ACEI Diuretics</td>
<td>Atrial tachycardia and fibrillation, β-Blockers CA (non-DHP)</td>
<td>Bradycardia, 2° or 3° heart block, β-Blockers† CA (non-DHP)</td>
</tr>
<tr>
<td>Myocardial Infarction ACEI (especially in systolic dysfunction)</td>
<td>Diabetes mellitus with proteinuria ACEI CA</td>
<td>Dyslipidemia, β-Blockers (non-ISA) Diuretics (high-dose)</td>
</tr>
<tr>
<td>Myocardial Infarction ACEI (especially in systolic dysfunction)</td>
<td>Diabetes mellitus (type II) Low-dose diuretics</td>
<td>Gout, Diuretics</td>
</tr>
<tr>
<td>Myocardial Infarction ACEI (especially in systolic dysfunction)</td>
<td>Dyslipidemia α-Blockers</td>
<td>Heart failure, β-Blockers (except carvedilol) CA (except amlopidine)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Carvedilol Losartan</td>
<td>Liver disease, Labetalol Methyldopa†</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>β-Blockers</td>
<td>Peripheral vascular disease, β-Blockers</td>
</tr>
<tr>
<td>Migraine</td>
<td>β-Blockers CA</td>
<td>Pregnancy, ACEI† All receptor blockers†</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Thiazide diuretics (not furosemide)</td>
<td>Renal insufficiency, Potassium-sparing agents</td>
</tr>
<tr>
<td>Preoperative hypertension</td>
<td>β-Blockers</td>
<td>Renovascular disease, ACEI All receptor blockers</td>
</tr>
<tr>
<td>Prostatin (BPH)</td>
<td>α-Blockers</td>
<td>Type I and II diabetes, β-Blockers High-dose diuretics</td>
</tr>
<tr>
<td>Renal insufficiency (caution in renovascular hypertension and creatinine → 3 mg/dl)</td>
<td>ACEI</td>
<td></td>
</tr>
</tbody>
</table>

*Conditions and drugs are listed in alphabetical order. † Contraindicated. ACE I = ACE inhibitors; CA = calcium antagonist; DHP = dihydropyridine; MI = myocardial infarction; nonCS = noncardioselective; ISA = intrinsic sympathomimetic activity; All = angiotensin II.

#### The Overall Plan of Therapy
As shown in Figure 3, therapy should usually be started with relatively small doses of a single agent, and then slowly titrating the dose to achieve the desired goal without inducing bothersome side effects from too much and too fast a fall in blood pressure.

#### The Need for Long-Acting Formulations
Whatever drug is chosen, it should be a long-acting formulation that provides 24-hour efficacy with a once-daily dose. As stated in JNC-6: “Long-acting formulations that provide 24-hour efficacy are preferred over short-acting agents for many reasons: 1) adherence is better with once-daily dosing; 2) for
some agents, fewer tablets incur lower cost; 3) control of hypertension is persistent and smooth rather than intermittent; and 4) protection is provided against whatever risk of sudden death, heart attack, and stroke that is due to the abrupt rise of blood pressure after arising from overnight sleep. Agents with an inherently long duration of action beyond 24 hours are attractive because so many patients inadvertently miss at least one dose of medication each week. Certain agents such as the CCB amlodipine and the ACEI trandolapril have sufficiently long durations of action so that they will continue to keep the blood pressure under reasonable control even if a dose is occasionally missed.

Combination Therapy
A rapidly growing group of fixed combination tablets of two different types of antihypertensive drugs are becoming available (10). The rationale for their use was stated in JNC-VI: “Combinations of low doses of two agents from different classes have been shown to provide additional antihypertensive efficacy, thereby minimizing the likelihood of dose-dependent side effects. Very low doses of a diuretic (e.g., 6.25 mg hydrochlorothiazide) can potentiate the effect of the other agent without producing adverse metabolic effects. Low-dose combinations with an ACE inhibitor and a nondihydropyridine calcium channel antagonist may reduce proteinuria more than either drug alone while inducing less pedal edema noted with the calcium channel antagonist alone (11). In some specific instances, drugs with similar modes of action may provide additive effects, such as metolazone and a loop diuretic in renal failure or a dihydropyridine and a nondihydropyridine calcium channel antagonist in hypertension (12)."

Some of these combinations, particularly those with very low doses of a diuretic, are indicated for initial therapy of hypertension. Most of them, however, should be reserved for the second choice in those patients who show only a partial response to the first choice.

Follow-up Care
As shown in Figure 3, JNC-6 recommends that “If blood pressure remains uncontrolled after 1 to 2 months, the next dosage level should be prescribed. It may take months to control hypertension adequately while avoiding adverse effects of therapy. Most antihypertensive medications can be given once daily, and this should be the goal in order to improve patient adherence. Home or office blood pressure measurement in the early morning before patients have taken their daily dose is useful to ensure adequate modulation of the surge in blood pressure after arising. Measurements in the late
Fig. 3. Management plan for mild hypertension. *If target organ damage is present, drug treatment is necessary at any level of blood pressure (BP) within the mild hypertension range. CV = cardiovascular; DBP = diastolic blood pressure; SBP = systolic blood pressure. (From ref. 4).

Initial blood pressure
DBP 90-105 or SBP 140-180 mmHg

Repeat BP measurement within 2-4 weeks + Lifestyle counselling

Within 4 weeks
BP < 140/90 mmHg

DBP 90-105 or SBP 140-180 mmHg

Evaluation of total CV risk*

Total CV risk low
DBP 90-95 and SBP 140-160 mmHg

Total CV risk high
DBP 95 or SBP 160 mmHg

Within 3-6 months
Follow-up
Drug treatment

DBP 90-95 and SBP 140-160 mmHg

DBP →95 or SBP →160 mmHg

DBP →90
SBP →140 mmHg

Follow-up Drug treatment

References


