UNIT NO. 5

TREATING HYPERTENSION AND TARGET ORGAN DAMAGE

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ABSTRACT

The impact of hypertension on the risk of the development of a cardiovascular event or death is directly proportional to the level of blood pressure i.e. its control. In addition, the presence of other risk factors further amplify its risk at any level of blood pressure. For hypertension treatment, the two most important issues are the choice of antihypertensive agents and the target/goal blood pressure attainment. An increasing number of trials have provided evidence that antihypertensive therapy that results in adequate blood pressure control provides some degree of cardiovascular, cerebrovascular and renal protection.

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INTRODUCTION

Hypertension is the one of the important major risk factor for premature cardiovascular, renovascular and cerebrovascular disease. Its prevalence being more common than cigarette smoking, dyslipidaemia, and diabetes in most countries. In the INTERHEART study, hypertension accounted for 18 percent of the population attributable risk of a first myocardial infarction.

The impact of hypertension on the risk of the development of a cardiovascular event or death is directly proportional to the level of blood pressure, i.e. its control. In addition, the presence of other risk factors further amplify its risk at any level of blood pressure. Moreover, the excess risk of a future adverse event attributable to hypertension is greater in individuals with established CVD, diabetes mellitus, or chronic kidney disease compared to those at lower risk. Therefore, target goal BP in these high-risk groups are different from those with uncomplicated hypertension (i.e. hypertension without end organ damage).

The 2003 Seventh Joint National Committee (JNC 7) report cited diabetes, chronic kidney disease, heart failure, ischemic heart disease and cerebrovascular disease as "compelling indications" for the treatment of hypertension. Other considerations include peripheral arterial disease (which is a form of vascular end organ damage) and traditional major coronary risk factors such as cigarette smoking and family history.

For hypertension treatment, the two most important issues are the choice of antihypertensive agents and the target/goal blood pressure attainment. An increasing number of trials have provided evidence that antihypertensive therapy that results in adequate blood pressure control provides some degree of cardiovascular, cerebrovascular and renal protection. However, the optimal level of control is unclear and varies with certain patient populations. In general, the benefits of increasingly intensive therapy must be weighed against the probable increased incidence of serious side effects associated with such a regimen.

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UNCOMPLICATED COMBINED SYSTOLIC AND DIASTOLIC HYPERTENSION

For patients with uncomplicated combined systolic and diastolic the goal of therapy is a blood pressure of <140/<90 mmHg. The treatment goals are determined by the higher BP category irrespective of systolic or diastolic readings.

ISOLATED SYSTOLIC HYPERTENSION

For hypertensive patients of all ages with an elevated systolic pressure (isolated systolic hypertension), the goal systolic pressure is <140 mmHg. However, the diastolic blood pressure should not be reduced to less than 65 mmHg in elderly patients to attain the target systolic pressure as symptoms of excessive end-organ hypoperfusion (e.g. giddiness or postural hypotension) may manifests in this subgroup. In such cases, the level of systolic blood pressure that is reached with two or three antihypertensive agents (even if greater than 140 mmHg) may be sufficient.

For hypertensive patients of all ages with an elevated diastolic pressure, the goal diastolic pressure is still less than 90 mmHg.

TYPE OF ANTIHYPERTENSIVE RX

There is no uniform agreement as to which antihypertensive drugs should be given for initial therapy for uncomplicated hypertensive patients. The major options are thiazide-type diuretics, Angiotensin converting enzyme (ACE) inhibitors/ angiotensin II receptor blockers (ARBs), Calcium channel blockers, and Beta blockers (now not recommended for initial therapy in the absence of a specific indication for their use).

Each of the antihypertensive agents is roughly equally effective in lowering the blood pressure, producing a good response in 40 percent of patients. However, there are wide interpatient and genetic/racial variability in patients response to one class of drug versus another.

INITIAL MONOTHERAPY

The goal of antihypertensive therapy in most patients with uncomplicated combined systolic and diastolic hypertension is a blood pressure of less than 140/90 mmHg.

A lower goal blood pressure, less than 130/80 mmHg, is indicated in patients with diabetes mellitus, proteinuric chronic kidney disease, and known atherosclerotic cardiovascular disease. Among patients with isolated systolic hypertension, the goal systolic pressure is less than 140 mmHg, but the diastolic blood pressure should not be reduced to less than 65 mmHg in elderly patients to attain the target systolic pressure.

Initial monotherapy is successful in most patients with mild essential hypertension. However, single drug therapy is unlikely to attain goal blood pressure in patients whose blood pressures are more than 20/10 mmHg above goal. In such cases, combination therapy using two drugs is needed.

CHOICE OF DRUG

Based on meta-analyses published in 2008 and 2009, the 2007 American Heart Association statement on the treatment of blood pressure in ischemic heart disease, and the 2007 European Society of Hypertension/European Society of Cardiology guidelines, these guidelines all concluded that the amount of blood pressure reduction is the major determinant of reduction in cardiovascular risk in both younger and older patients with hypertension, not the choice of antihypertensive drug (assuming that the patient does not have an indication for a particular drug, such as diltiazem, verapamil, or a beta blocker for rate control in atrial fibrillation).

This conclusion was based upon the findings that, at the same level of blood pressure control, most antihypertensive drugs provide the same degree of cardiovascular protection. The CAPPP, STOP-Hypertension-2, NORDIL, UKPDS, and INSIGHT trials found little overall difference in outcomes between older (such as diuretics and beta blockers) and newer antihypertensive drugs (such as ACE inhibitors and calcium channel blockers) and the CAMELOT trial found no significant difference in outcomes between amlodipine and enalapril therapy. However, some patients may have an indication for a specific drug that is unrelated to essential hypertension (e.g. a nondihydropyridine calcium channel blocker like diltiazem or beta blocker for rate control in patients with atrial fibrillation).

In the absence such specific indications, thiazide diuretics, long-acting calcium channel blockers (most often a dihydropyridine), and ACE inhibitors or angiotensin II receptor blockers (ARBs) can be used. Beta blockers are not commonly used nowadays for initial monotherapy in the absence of a specific indication. They may have an adverse effect on some cardiovascular outcomes, particularly in older patients.

HYPERTENSION WITH DIABETES MELLITUS OR PROTEINURIC KIDNEY DISEASE

For diabetic patients and chronic renal disease, the JNC 7 report and most guidelines suggest a goal blood pressure of <130/80 mmHg. This is the ideal goal BP in patients with diabetes mellitus and patients with chronic kidney disease with proteinuria (i.e. Defined here as more than 500mg of protein per day). However there is little data supporting a lower blood pressure goal for renal protection in patients without proteinuria. Among patients in whom there is a reasonable likelihood of requiring a second drug a long-acting ACE inhibitor/ARB or a long-acting dihydropyridine calcium channel blocker, can be added if additional therapy is required to achieve the desired combination regimen.

For patients with known atherosclerotic cardiovascular disease a goal blood pressure of <130/<80 mmHg in patients is ideal.

PATIENTS WITH KNOWN CVD OR CORONARY RISK EQUIVALENT

The placebo-controlled trials published after JNC 7 (JNC 8 is scheduled to be released in end 2010), provide some support (HOPE and EUROPA trials) for a BP goal less than 130/80 mmHg in patients with atherosclerotic cardiovascular disease.

Despite the limited confirmatory data from randomized trials, a goal BP of less than 130/80 mmHg was recommended in patients with atherosclerotic cardiovascular disease in the 2007 American Heart Association statement on the treatment of blood pressure in ischemic heart disease. Atherosclerotic cardiovascular disease was defined as established coronary artery disease or a coronary risk equivalent (carotid artery disease, peripheral arterial disease, or abdominal aortic aneurysm). The same goal was set for individuals with diabetes or chronic kidney disease, which are also considered coronary risk equivalents.

For patients with CVD without heart failure, it is possible that a lower limit exists for desirable diastolic pressure because much of coronary filling occurs during diastole. Observations from the Framingham study and the INVEST trial suggested an increase in risk for patients with CVD at a diastolic pressure below 70 to 75 mmHg.

J SHAPED CURVE

The lowest desirable blood pressure for patients with CVD was not evaluated in the trials, and only limited information exists to define such a lower limit. It has been suggested amongst some cardiologists that cardiovascular risk might increase (J shaped curve) if the blood pressure were gradually lowered too much within the physiologic range.

HEART FAILURE

For patients with heart failure due to systolic dysfunction, the goal of therapy is the lowest blood pressure that is not associated with symptoms of hypotension or evidence of hypoperfusion (e.g., worsening prerenal azotemia). In some patients with severe HF, this may be a systolic pressure as low as 90 mmHg. Most patients with systolic HF are treated with inhibition of the renin-angiotensin system (e.g. angiotensin converting enzyme

inhibitors or angiotensin II receptor blockers), beta blockers, and, in some patients, an aldosterone antagonist. These agents have favorable effects on survival that are independent of their effects on blood pressure.

ISOLATED SYSTOLIC HYPERTENSION

Although there are no convincing data, there may be a threshold diastolic BP below which adverse cardiovascular outcomes might increase in elderly patients with isolated systolic hypertension. Guidelines like JNC 7 suggest a minimum post treatment diastolic pressure of 60 mmHg overall or perhaps 65 mmHg in patients with known coronary artery disease unless symptoms that could be attributable to hypoperfusion occur at higher pressures.

PRIOR STROKE

The efficacy of lowering the BP with antihypertensive therapy has been evaluated in patients with a prior stroke, many of whom have a history of prior hypertension. Blood pressure control over the long-term is likely to significantly reduce the risk of recurrent stroke and other cardiovascular events.

The 2006 American Heart Association/American Stroke Association Guidelines recommend antihypertensive therapy for all patients with a stroke and TIA, and recommend the use of diuretics and the combination of diuretics and an ACE inhibitor, but do not provide target blood pressure goals. There is a progressive increase in risk for cardiovascular events with rising blood pressure above 115/75 mmHg but benefit from therapy initiated when the blood pressure is <130/80 mmHg has not been established. This it is reasonable to initiate antihypertensive therapy in individuals with blood pressure ≥130/80 mmHg after they have been stabilised following a stroke.

HYPERTENSION WITH LVH

ARBs here may have specific benefit in severe hypertension with ECG evidence of left ventricular hypertrophy although it is highly likely that an ACE inhibitor is equally effective.

Regardless of the goal BP, blood pressure reduction should be gradual in all patients in the absence of a hypertensive emergency. Patients with isolated systolic hypertension or stenotic arterial lesions (carotid, renal, coronary) may be at increased risk for ischemic manifestations at lower blood pressure goals. Thus, such patients should be monitored carefully for signs of hypoperfusion such as neurologic dysfunction or elevations in serum creatinine.

All antihypertensive therapy should be accompanied by recommended management of other risk factors.

PATIENTS AT HIGH RISK FOR CVD

The optimal goal blood pressure target for patients at high risk for CVD but without established CVD, diabetes, or chronic kidney disease was addressed in the 2007 guidelines from the AHA and ESH/ESC. The target blood pressure is less than 130/80 mmHg in high-risk patients. High risk patients are defined here as those with a ten year Framingham/ATP III risk score ≥10 percent(or the presence of one or more of the following: three or more conventional cardiovascular risk factors, the metabolic syndrome. However, the blood pressure reduction should be gradual, particularly in older patients. A goal blood pressure less than 130/80 mmHg is ideal but not mandatory in such patients. In order to slow the progression of kidney disease among patients with proteinuric chronic kidney disease, antihypertensive therapy with ACE inhibitors or ARBs and other drugs as necessary to lower the blood pressure to less than 130/80 mmHg in an attempt to slow the rate of disease progression.

MONOTHERAPY

The likelihood of a good response is increased when two simple clinical characteristics, age and race, are utilized to determine drug treatment. Younger patients respond best to angiotensin converting enzyme (ACE) inhibitors or angiotensin-II receptor blockers (ARBs) and beta blockers. However, beta blockers are not commonly used for initial monotherapy in the absence of a specific indication because of a possible increase in cardiovascular events, particularly in older patients. Compared to other antihypertensive drugs in the primary treatment of hypertension, beta blockers may be associated with a higher rate of stroke (particularly among smokers). These effects are primarily seen in patients over age 60. Beta blockers are also associated with impaired glucose tolerance and an increased risk of new onset diabetes with the exception of vasodilating beta blockers such as Carvedilol and Nebivolol.

Black and elderly patients often respond best to a thiazide diuretic or long-acting calcium channel blocker. However, many elderly hypertensive patients have a specific indication for an ACE inhibitor or ARB, including heart failure, prior myocardial infarction, and proteinuric chronic kidney disease.

SEQUENTIAL MONOTHERAPY

Each of the recommended first-line agents will normalise the BP in 40 percent of patients with mild hypertension. A patient who is relatively unresponsive to one drug has an almost 50 percent likelihood of becoming normotensive on a second drug. Thus, in a patient who has little or no fall in BP after starting on a drug, switching to (rather than adding) another class of drug may allow as many as 60 to 80 percent of patients with mild hypertension to initially be controlled with a single agent.

This regimen of trying to find the one drug to which the patient is most responsive may minimize side effects, maximize patient compliance, and is as effective as some forms of combination therapy. However, over time, more than one drug will be needed in many patients who are initially controlled due

to tachyphylaxis. Thus, drugs that are longer acting are preferred and it is necessary to check the morning BP prior to the next dose whenever a once daily regimen is used.

COMBINATION THERAPY

There are two issues related to combination therapy: use as first-line therapy; and addition of a second drug when the goal blood pressure is not achieved with monotherapy. Recommendations for combination therapy were made in the 2003 JNC 7 report, the 2004 British Hypertension Society guidelines, and the 2007 European Societies of Hypertension and Cardiology guidelines. Administering two drugs as initial therapy should be considered when the blood pressure is more than 20/10 mmHg above goal, as recommended in the JNC 7 report. This strategy may increase the likelihood that target blood pressures are achieved in a reasonable time period. Fixed-dose combination preparations are available that may improve patient compliance and reduce its side effects. The use of a long-acting dihydropyridine calcium channel blocker plus a long-acting ACE inhibitor/ARB (such as amlodipine plus benazepril is often used based on trials results (ACCOMPLISH trial).

LEARNING POINTS

- **For patients with uncomplicated combined systolic and diastolic the goal of therapy is a blood pressure of <140/<90 mmHg.**
- **For hypertensive patients of all ages with an elevated diastolic pressure, the goal diastolic pressure is still less than 90 mmHg.**
- **Single drug therapy is unlikely to attain goal blood pressure in patients whose blood pressures are more than 20/10 mmHg above goal. In such cases, combination therapy using two drugs is needed.**
- **For patients with known atherosclerotic cardiovascular disease a goal blood pressure of <130/<80 mmHg in patients is ideal.**
- **For patients with heart failure due to systolic dysfunction, the goal of therapy is the lowest blood pressure that is not associated with symptoms of hypotension or evidence of hypoperfusion (e.g., worsening prerenal azotemia).**
- **Regardless of the goal BP, blood pressure reduction should be gradual in all patients in the absence of a hypertensive emergency.**