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Hypertension (blood pressure [BP] > 140/90 mmHg) remains the most important modifiable antecedent of adverse cardiovascular and renal events and cognitive dysfunction (vascular and Alzheimer's dementia) [1]. Due to the rising epidemics of obesity and diabetes mellitus within the next two to three decades, the hypertension-associated disease burden is predicted to increase [2].

Epidemiological and observational studies demonstrate that the higher the BP, the greater the risk [1]. Death from cardiovascular events doubles with every 20 mmHg increase in systolic BP over the range of 115-185 mmHg or each 10 mmHg increase in diastolic BP over the range of 75-115 mmHg [1]. Systolic BP is a more robust risk indicator and is therefore a more important therapeutic target than diastolic BP, especially in subjects older than 50 years [1].

Abundant clinical trial evidence has shown that antihypertensive therapy significantly reduces the risk of cardiovascular events : stroke by 35-40%, myocardial infarction by 20-25% and heart failure by > 50%, with larger BP reductions associated with greater reductions in risk [3-4].

However, despite these clinical therapeutic successes, the control of BP in clinical community practices remains inadequate and suboptimal [5-6].

Several factors have been proposed to explain this poor BP control rate [5-6]. Lack of 1) adherence of physicians and other health care providers to hypertension guidelines promulgated by national and international scientific organizations, and 2) awareness and impact of information from recent clinical trials, play an important role.

DETERMINANTS OF OPTIMAL BPCONTROL

The management of a hypertensive patient is a complex process that blends focus BP control efforts with complementary strategies to manage variable complicated patterns based on the presence of risk factors and/or

target organ involvement that complicate the therapeutic approaches. Therefore the management of a hypertensive patient should be both "personalized" based on his associated condition and achievement of the target BP established by hypertension guidelines [7].

GUIDELINES FOR INITIATION AND MANAGEMENT OF THE HYPERTENSIVE PATIENT

Initiation of antihypertensive drug therapy is based on three criteria :

1. Levels of systolic and diastolic blood pressures
2. Rapidity (promptness) and aggressiveness of BP reduction to reach target BP goals.
3. Cardiovascular risk status of the patient.

1. Levels of systolic and diastolic blood pressures

Although hypertension is defined as BP 140/90 mmHg, before addressing the question "When should drug therapy be started ?" one caveat must be always recalled : an elevated BP above 140 mmHg systolic or 90 mmHg diastolic, must always be remeasured at least three times over at least four weeks to ensure that hypertension is present.

Hypertension guidelines recommend initiation of antihypertensive drug therapy at BP 140/90 mmHg [1]. In addition to systolic and diastolic BP levels, risk factors, target organ damage and presence of overt clinical disease (Table I) are used to determine the degree of risk, using a stratification chart to classify risk from average to high [1]. In turn, the level of risk is used to decide upon the need to begin therapy or to continue to monitor [1].

In patients with grade 1 (BP = 140-159/90-99 mmHg) and grade 2 (BP = 160-179/100-109 mmHg) hypertension, antihypertensive drug therapy should be initiated promptly in patients classified as high or very high risk [8]. However, in patients at moderate or low "added risk BP" as well as having other cardiovascular risk factors the effect of nonpharmacologic treatment should be evaluated for an extended period of three to 12 months [8]. If after this extended observation period, BP 140/90 mmHg persists, antihypertensive drug therapy should be initiated in patients at moderate risk and considered in patients at lower risk [8]. In patients with grade 3 (BP > 180/110 mmHg), the elevated BP should be confirmed within a few days, and drug therapy initiated even without waiting to establish the absolute risk [8]. Complete assessment of other risk factors, target

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TABLE I
DETERMINANTS OF CARDIOVASCULAR RISK STATUS*

CARDIOVASCULAR RISK FACTORS

- > Levels of systolic and diastolic blood pressure
- > Age
 - Men > 55 years
 - Women > 65 years
- > Smoking
- > Dyslipidemia
- > Family history of premature cardiovascular disease
 - Men < 55 years
 - Women < 65 years
- > Abdominal (central) obesity
 - Men 102 cm
 - Women > 88 cm
- > Diabetes mellitus
- > Target organ disease
- > Left ventricular hypertrophy
- > Renal insufficiency
- > Microalbuminuria

ASSOCIATED CLINICAL CONDITIONS

- > Cerebrovascular disease
- > Heart disease
- > Renal disease
- > Peripheral vascular disease
- > Advanced retinopathy

*Modified from *J Hypertension* 2003 ; 21 : 1011-1053.

organ damage or associated clinical disease can be performed after initiation of treatment.

For patients with *prehypertension* (BP = 130-139/80-89 mmHg) antihypertensive drug treatment is recommended only for those with stroke, coronary artery disease, diabetes mellitus, chronic renal disease or if total cardiovascular risk status is high [9, 11]. In contrast, in patients at moderate or low total risk only, close monitoring of BP with nonpharmacologic lifestyle measures associated with correction of cardiovascular risk factors is indicated.

2. Effect and importance of promptness and aggressiveness of optimal BP control

In addition to BP goal attainment itself, the time to BP control should be considered [4]. The achievement of BP control has emerged as a goal of treatment based on findings of recent clinical trials such as VALUE (Valsartan Antihypertensive Long-term Use Evaluation) and the systolic hypertension in Europe (Syst-Eur) trials [12-13].

The VALUE trial of cardiovascular events in hypertension was designed to compare treatment initiated with an angiotensin receptor blocker (ARB) valsartan, with treatment initiated with calcium channel blocker (CCB) amlodipine [12].

Blood pressure control was not equivalent when comparing both arms of the trial. The differences in achieved blood pressure was particularly extreme during the early titration phase of the trial, during the first six months, but persisted throughout. One month into the trial, systolic blood pressure was 4 mmHg lower in those treated with amlodipine monotherapy 5 mg/D compared to initial therapy with valsartan 80 mg/D. By six months, systolic blood pressure was still 2 mmHg lower in the amlodipine-treated patients. Consistent with the differences in blood pressure lowering efficacy between the two treatment arms, 32% still had a systolic blood pressure

160 mmHg on valsartan at one month compared to 23% on amlodipine and, by six months, the percentages still differed significantly (13.2 versus 8.3% respectively). By study end, systolic blood pressure control (< 140 mmHg) was achieved in 58% of those receiving valsartan compared to 64% of those receiving amlodipine, and the combined systolic and diastolic target of < 140/90 mmHg was achieved in 56 and 62%, respectively.

Looking more closely at the data for the first six months of the VALUE trial, major differences in endpoint rates between the two treatment arms appear to occur early in the trial, when there was the greatest disparity in blood pressure control. A comparison of patients with systolic blood pressure controlled to < 140 mmHg by six months with those in whom systolic blood pressure was not controlled confirms that prompt and better blood pressure control was associated with a 25% reduction at primary end point, a 45% reduction in stroke, a 24% reduction in myocardial infarction, a 21% reduction in all-cause death and a 34% reduction in heart failure hospitalization [12]. This was true irrespective of treatment allocation and strongly supports the view that it is the quality of blood pressure control that determines the benefit of treatment [4]. Moreover, VALUE adds more by suggesting that prompt blood pressure control defines a population at lower risk of subsequent events and that this should be an objective of modern therapy. Thus, it is possible that “the speed to blood pressure control might define benefit, rather than drive benefit”.

Thus VALUE provides further powerful confirmation of the importance and supremacy of blood pressure control, as well as novel data demonstrating the importance of achieving optimal blood pressure control as early as possible. In this regard, the most effective treatment strategy is likely to be that which achieves the most effective blood pressure control [4].

Similar findings were observed in the *Syst-Eur trial* [13]. The 4-year open-label extension of the double-blind placebo-controlled Syst-Eur trial in hypertensive patients aged 60 years and older offered an opportunity to compare immediate therapy (persons in the active-treatment arm of the double-blind study) with delayed therapy (persons in the placebo arm of the double-blind trial who started active therapy in the extension trial) [13]. Immediate antihypertensive therapy was associated with a 28% reduction in the relative risk of stroke and a 15%

reduction in cardiovascular complications [13]. These risk reductions were entirely due to the significant benefits associated with initiation of active treatment immediately after randomization during the double-blind phase of the study ; there were no between-group differences in any end points during the extension trial [4, 13].

In conclusion, these two clinical trials provide strong support for effective and prompt BP reduction for the prevention of cardiovascular outcomes especially in high risk hypertensive patients.

3. Management of cardiovascular risk status

The primary goal of treatment of the patient with high BP is to achieve the maximum reduction in the long-term total risk of cardiovascular morbidity and mortality. This requires treatment of all reversible risk factors identified including smoking dyslipidemia or diabetes mellitus and the appropriate management of associated clinical conditions, as well as raised BP per se [1, 8].

BLOOD PRESSURE TARGETS

In the light of current evidence from clinical trials, it is recommended to reduce BP intensively at least below 140/90 mmHg and to lower values, if tolerated. In the *HOTstudy*, the only clinical trial not exclusively involving diabetes suggests that, except in smokers, a reduction of diastolic BP to an average of 82 mmHg rather than 85 mmHg significantly reduces major cardiovascular events in nondiabetic patients at high/very high risk as well as in patients with previous ischemic heart disease, in those older than 65 years and in women [14]. In chronic kidney disease, better protection from progression to endstage renal failure was seen only in patients with proteinuria greater than 1 g/D at an achieved BP of 125/75 mmHg compared to 135/82 mmHg [15]. In patients with a history of stroke or transient ischemic attack, the *PROGRESS Trial* showed less cardiovascular morbidity and mortality by reducing diastolic BP to 79 mmHg (active treatment group) rather than 83 mmHg (placebo group) [9]. Similar observations have been made in patients with coronary artery disease [16]. Regarding systolic BP, evidence of greater benefit from a more rigorous reduction in systolic BP is limited to the *UK Prospective Diabetes Study Group* (UKPDS) which has shown less cardiovascular events at values below systolic BP of 130 mmHg and 120 mmHg as compared to 140 mmHg [17].

COMBINATION ANTIHYPERTENSIVE DRUG THERAPY

The need to achieve more prompt BP control in high-risk hypertensive patients requires multiple antihypertensive drug therapy and quicker adjustment of doses [18]. Patients with uncontrolled BP should be followed up and medications adjusted at least monthly until the

goal BP is attained ; those with stage 2 hypertension or complicating comorbid conditions should be followed up more frequently [4]. After the BP goal is attained, the patient should be followed up at 3 to 6 months intervals to ensure that desirable BP levels are maintained [1, 4].

In terms of multiple drug therapy fixed dose combination of two medications affords advantages over the use of two agents separately [4] :

1. To overcome physicians inertia and the tendency to accept higher than recommended BP levels in their patients ;
2. More useful in patients with diastolic BP minimally above goal and systolic BP substantially above goal as is frequently observed in elderly hypertensive patients ;
3. Better control of both systolic and diastolic blood pressures simultaneously and promptly ;
4. Shorter time to achieve goal BP levels [19].

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