33 *Paradigm Shift in Management of Hypertension*

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Abstract: High blood pressure is among the most important preventable causes of death worldwide and the treatment of hypertension is a key strategy for primary prevention of CV disease. β blockers have been used widely in the treatment of hypertension..

In comparison with other antihypertensive drugs, the effect of β blockers is less than optimum, with a raised risk of stroke. Hence, it is recommended that β blockers should not remain first choice in the treatment of primary hypertension and should not be used as reference or first line drug in hypertensive emergency.

An analysis of the outcome of the LIFE trial and ASCOT-BPLA trial showed convincing evidence for ARBs, and CCB with ACEI for multiple CV benefits apart from reducing the incidence of new-onset diabetes compared to beta-blockers. Treatment of hypertension is driven by guidelines. Guidelines are driven by evidence and the substantial evidence base for treating hypertension, is highlighted by NICE/BHS guidelines. NICE guidelines have focused almost exclusively on the treatment of older people with established target organ damage or concomitant disease. NICE also recommended ACEI was likely to be a more effective initial therapy than CCB or thiazide-type diuretic in younger patients. With the available evidence and recommendations from international societies on hypertension guidelines, we are witnessing a paradigm shift in management of hypertension. Beta-blocker and hypertension should not be considered in isolation. Other co-existing CV risk factors have to be treated simultaneously to get maximum benefit from CV disease protection.

Hypertension remains the most common risk factor for cardiovascular morbidity and mortality (Fig. 33.1).[1] Hypertension is among the most important preventable causes of death worldwide. The treatment of hypertension is a key strategy for primary prevention of CVD.[2,3]

Despite massive efforts to identify and treat hypertension less than a third of individuals with a usual BP exceeding 140/90 mmHg are adequately treated. Even in individuals whose hypertension is well controlled less than a third are protected from subsequent strokes and heart attacks.[4,5] With the recognition that risk increases linearly even in high-normal ranges in BP (Fig. 33.2)[6] the need for assessment going beyond BP values and using individuals absolute overall CV risk as the criterion for therapy has become obvious.[7]

AGEING AND ISOLATED SYSTOLIC HYPERTENSION (ISH)

The systolic blood pressure increases with age as the aorta stiffens so that 90% of Americans still having a healthy blood pressure at age 55 years will have hypertension when they reach age 75 years.[8] This systolic upswing is world -wide[9] (Fig. 33.3).

RECENT HYPERTENSION TRIALS

Debate has been going on for several years about whether the mortality and morbidity benefits of treating hypertension with pharmacotherapy can be attributable exclusively to the reduction in risk from lowering blood pressure per se, or whether certain drugs confer additional CV benefits owing to effects not directly associated with their antihypertensive efficacy.[10,11] In particular, the claims that interfering with the renin-angiotensin system might be beneficial in patients at risk has been widely publicized and discussed. Studies such as CAPP (Captopril Prevention Project)[12] HOPE (Heart Outcomes Prevention Evaluation)[13] and EUROPA (European Trial on Reduction of Cardiac Events with perindopril in stable coronary artery disease)[14] have claimed benefits for angiotensin-converting- enzyme inhibitors not related to blood-pressure lowering. LIFE (Losartan Intervention for Endpoint reduction in hypertension) trial[15] reported greater beneficial effects on stroke from the angiotensin receptor blocker losartan than from the comparator substance, the β-blocker atenolol. However, not all trials claiming benefits were blood-pressure trials. Several compared active treatment with placebo, and in other it is unclear to what extent the effects were benefits from the inhibitor of the renin-angiotensin system rather than negative influences of the comparator substances.

Two meta-analyses of the multiple randomized controlled trials that closed before mid-2003[4,5] came to the conclusions: (1) Blood-pressure reduction by any drug compared with placebo reduced cardiovascular morbidity and mortality; (2) All classes of drugs reduced total and cardiovascular mortality equally; and (3) Different classes provided differing degrees of protection against individual cardiovascular morbidities. Specifically, the ALLHAT (Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) study[16] compared three initial therapies: diuretics, calcium-channel blocker, and angiotensin-converting-enzyme (ACE) inhibitors, and showed no difference between treatments on fatal coronary heart disease, nonfatal myocardial infarction, or all-cause mortality. Hence, most national and international guidelines recommend initial diuretic therapy, even though the incidence of diabetes rose in the diuretic group of ALLHAT. Review by Staessen and colleagues,[5] most trials comparing different classes of drugs, small but clinically significant differences in blood pressure were seen, which probably contributed to the possible advantage of one substance over another.

Should β Blockers Remain First choice in the Treatment of Primary Hypertension?

A meta-analysis: β blocker treatment of patients with primary hypertension was associated with a substantially higher risk of stroke than treatment with other antihypertensive agents. Because β blockers lower blood pressure to the same extent as other antihypertensive agents, the question arises about possible mechanisms to explain why their preventive effect is not as good as other antihypertensive drugs. β blockers have effects on both glucose and lipid metabolism that theoretically could increase the risk of CVD.[17,18] Regression of left ventricular hypertrophy is also more closely correlated with central blood pressure than brachial blood pressure,[19] which could explain the less beneficial effect on left ventricular hypertrophy of β blockers as compared with other antihypertensive drugs.[20] The outcome of the ASCOT-BPLA trial[21] showed a stroke reduction close to that seen in LIFE (23 vs 25%),[22] where treatment based on a calcium antagonist was given instead of a treatment based on a β blocker. Moreover, in comparison with other antihypertensive drugs, the effect of β blockers is clearly suboptimum with a higher risk of stroke. Hence, β blockers should not remain as first choice in the treatment of primary hypertension.

Two additional facts were recorded: first, the commonly used β blocker, atenolol, provided no cardioprotection;[23] second, diuretic-based regimens with or without β blocker provoked more new cases of diabetes than comparator regimens (Table 33.1).[24,25] Overall, these studies question the wisdom of initial therapy with a

β blocker, especially in combination with a high dose of diuretic. The effect of β blocker is drug specific to atenolol or is a class effect needs to be critically evaluated. Whether the effect of β blocker is drug specific to atenolol or is a class effect needs to critically evaluated.

ANGLO-SCANDINAVIAN CARDIAC OUTCOMES TRIAL (ASCOT-BPLA)- BLOOD PRESSURE LOWERING ARM: A MULTICENTRE RANDOMIZED CONTROLLED TRIAL

Background: The apparent shortfall in prevention of CHD noted in early hypertension trials has been attributed to disadvantages of the diuretics and β blockers used. For a given reduction in blood pressure, some suggested that newer agents would confer advantages over diuretics and β blockers.

Aim was to compare the effect on nonfatal myocardial infarction and fatal CHD using combinations of atenolol with a thiazide versus amlodipine with perindopril

Endpoints for amlodipine and Perindopril versus atenolol and thiazide (ASCOT trial) (Table 33.2).

The trial clearly shows that the amlodipine-based regimen prevented more major cardiovascular events and induced less diabetes than the atenolol-based regimen. On the basis of previous trial evidence, these effects might not be entirely explained by better control of blood pressure. The results have implications with respect to optimum combinations of antihypertensive agents.

ASCOT-BPLA has shown that blood pressure can be lowered effectively in most patients. Furthermore, the preferential reduction in cardiovascular events associated with an antihypertensive regimen of a calcium-channel blocker (amlodipine) with addition of perindopril if necessary, particularly when used in combination with effective lipid lowering,[27] results in the prevention of most major cardiovascular events associated with hypertension. These results will help clinicians to greatly reduce CV disease to which patients with hypertension are exposed.

MANAGEMENT OF HYPERTENSION AND DYSLIPIDEMIA (ASCOT-LLA)

Recent large-scale blood pressure and lipid-lowering trials continue to redefine and challenge our perceptions of how to optimally manage CVD. Current evidence suggests that high-risk patients should be treated with an aggressive blood pressure-and lipid-lowering strategy. The lipid-lowering arm of the (ASCOT-LLA) trial demonstrated that lowering cholesterol levels with atorvastatin 10 mg provided additional benefit, over and above hypertensive therapy.

Conduit Artery Function Evaluation (CAFÉ) Study: (CIRCULATION. 2006; 113: AND NA).

Differential Impact of Blood Pressure-Lowering Drugs on Central Aortic Pressure and Clinical Outcomes

CAFÉ study, a sub study of the ASCOT, examined the impact of 2 different BP lowering-regimens (atenolol ± thiazide-based versus amlodipine ± perindopril-based therapy) on derived central aortic pressures and hemodynamics. The results show that brachial blood pressure is not always a good surrogate for the effect of blood pressure-lowering drugs on arterial hemodynamics. In the CAFÉ study, atenolol ± thiazide-based treatment was much less effective than amlodipine ± perindopril-based treatment at lowering central aortic pressures. These findings suggest a mechanism to support recent meta-analyses that have challenged the recommendation for β blockers as an optimal treatment for uncomplicated hypertension.

British Hypertension Society:
NICE Guidelines

Now there is much interest in the updated recommendations for the drug treatment of hypertension issued by the UK's National Institute for Health and Clinical Excellence (NICE) working in collaboration with the British Hypertension Society (BHS)

A systematic search of the literature was performed by NICE guideline developers concentrating on RCTs comparing any combination of antihypertensive drugs from among the following five classes of drugs:

- ACE inhibitors (ACEi)
- Angiotensin-II receptor antagonists (ARB)
- Beta-receptor blockers (BB)
- Calcium-channel blockers (CCB)
- Thiazide-type diuretics (TD).

There are three important developments in this guideline:

1. A reappraisal of the role of β blockers
2. The first formal cost-effectiveness analysis
3. Stratification of the initial selection of drug treatment according to age.

Angiotensin-II Receptor Antagonists versus β-blockers

One study (LIFE) was found comparing the angiotensin-II receptor antagonist (ARB) losartan with the β-blocker atenolol as first-line antihypertensive therapy.

The study found no significant difference between the two treatments in terms of myocardial infarction, revascularization procedures, heart failure or angina. However, the study did find ARBs to be associated with a reduced incidence of stroke new-onset diabetes and fewer study drug withdrawals.

Calcium-channel Blockers versus β-blockers

A meta-analysis of three studies (ASCOT, ELSA, INVEST) compared calcium-channel blockers (CCBs) with β-blockers. There was no statistically significant difference in mortality or myocardial infarction. Based on the results of the two studies reporting stroke as on outcome (ASCOT, ELSA) CCBs were associated with a reduced incidence of stroke.

Outcomes in those with Isolated Systolic Hypertension (ISH)

A meta-analysis of three randomized controlled trials (SHEP, SHEP-P, SYST-EUR) compared active antihypertensive drug therapy using either thiazide-based diuretics or a calcium-channel blocker with placebo in patients with ISH. Antihypertensive drug therapy was associated with a reduced incidence of stroke although there was no statistically significant difference in mortality rate. Based on the results of another subgroup analysis of patients with ISH from a randomized-controlled trial involving patients with hypertensive LVH, initial therapy with an ARB is associated with a reduced incidence of stroke and a lower mortality rate compared to initial anti-hypertensive therapy with a β-blocker.

Outcomes in Younger Patients

The literature search found no evidence for the clinical outcomes. Therefore, blood pressure response to drug therapy was used as a surrogate. ACE inhibitors and beta-blockers as more effective at lowering blood pressure in younger people, when compared to calcium channel-blockers or thiazide-type diuretics.

NICE: A Revolution in Guidelines

Most focus will be on appropriate decision to relegate β blockers as a less suitable initial therapy for the routine treatment of hypertension because they are less effective than other drug choices at preventing major cardiovascular events, especially stroke.[28,29] Beta-blockers are also more likely to induce the development of diabetes and have an unfavorable effect on the metabolic profile, especially in combination with diuretics.[30] Thus, β blockers were the least cost-effective treatment opinion for most people with hypertension.[28] Whether this conclusion applies to all β blockers, or only those used in clinical trials of hypertension (mainly atenolol) is unknown (Table 33.3).

Current Role of β-blockers

Beta-blockers are not a preferred initial therapy for hypertension. However, β-blockers may be considered in younger people, particularly:

- Those with an intolerance or contraindication to ACE inhibitors and angiotensin-II receptor antagonists
- Women of childbearing potential, or
- Patients with evidence of increased sympathetic drive.

In these circumstances, if therapy is initiated with a β-blocker and a second drug is required, add a calcium-channel blocker rather than a thiazide-type diuretic to reduce the patient's risk of developing diabetes. In patients whose BP is well-controlled (i.e., 140/90 mmHg or lower) with a regimen which includes a β blocker, there is no absolute need to replace the β blocker with an alternative agent. When a β blocker is withdrawn, the dose should be stepped down gradually. Beta-blockers should not be withdrawn in patients with compelling indications.

Specific Indications for Various Classes of Antihypertensive Drugs

Recommendations for certain drugs to be used for certain compelling indications (Table 33.4)[31] seem appropriate for clinical decision making. However, practitioners should realize that head-to-head comparisons in any cardiovascular-renal disease have been inadequate in recording these special benefits. Moreover, many patients carry several compelling indications and the best advice is to reduce the blood pressure to the appropriate goal with whatever is needed while avoiding adverse effects.

CONCLUSIONS

We have witnessed much progress in our understanding about pathophysiological mechanisms of hypertension and its complications. Based on available convincing evidence, the recommendations are made by international organizations. We, as clinicians, should change our approach in managing people with hypertension based on evidence. Really there is a paradigm shift in the management of hypertension which, if implemented, would help to bring down the morbidity and mortality due to CV diseases.

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