Combination therapy for hypertension

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The benefit of lowering blood pressure

Raised blood pressure is associated with significant cardiovascular morbidity and mortality, yet there is no demarcated cut-off point of blood pressure that clearly separates normotensive from hypertensive individuals. In fact, from an epidemiological perspective, new data from one million adults, including 61 prospective observational trials, the relationship of blood pressure is liniar down to systolic blood pressure (SBP) of 115 mmHg and a diastolic blood pressure (DBP) of 75 mmHg.[1]

It is clear from this data, that for every increase of 20 mmHg in systolic pressure or 10 mmHg increase in diastolic pressure, cardiovascular risk is doubled (see Figure I). This study also demonstrates that if SBP can be decreased by 20 mmHg or DBP decreased by 10 mmHg, the cardiovascular risk can be halved. The message is clear:

Lowering of Blood Pressure is all-important.

Moreover, there is no blood pressure threshold below which benefits cease, down to the level of $^{115}/_{75}$ mmHg.

Treatment options for hypertension

Since 1993 [JNC V Report], recommendations for the clinical management of hypertension have been made.

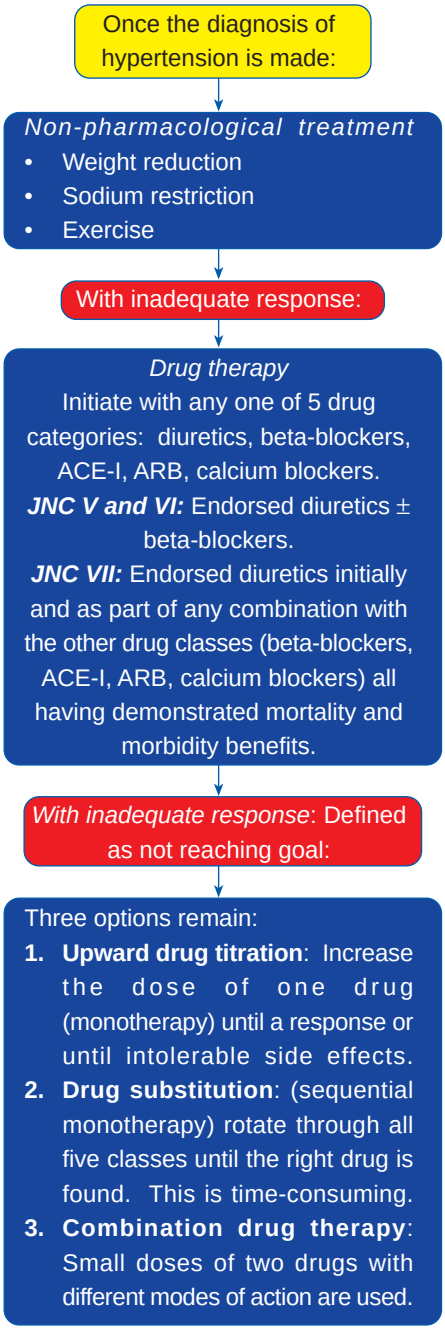
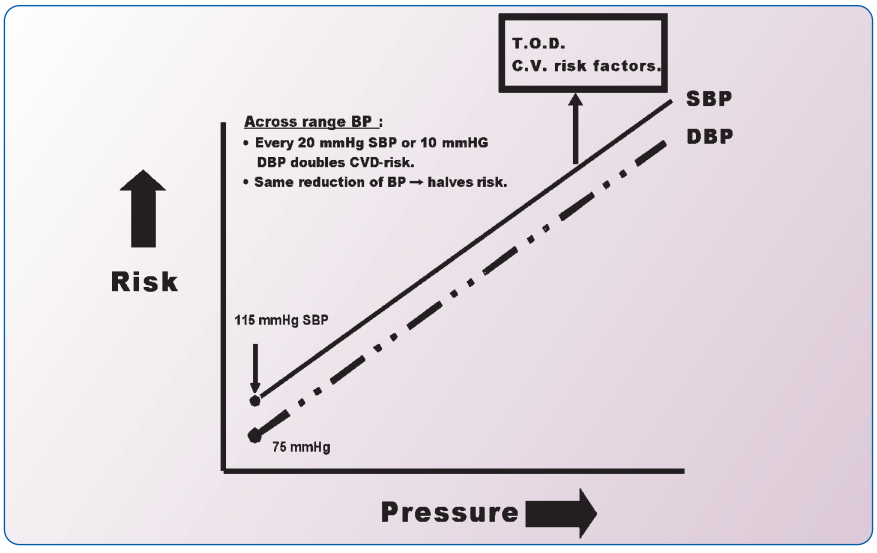


Figure 1: Relationship: Blood pressure and cardiovascular risk:



T.O.D. = Target organ damage and the presence of other cardiovascular risk factors will increase the risk of any given blood pressure level.

Today, many experts see to initiate drug therapy for hypertension and not only as an option when monotherapy failed.

Indications for combination therapy:

1. To achieve goal blood pressure in hypertension:

i. Combination therapy will be needed in many (or most) hypertensive patients to achieve optimal blood pressure levels. Fewer than 50% of hypertensive patients are able to achieve their blood pressure goal with the use of any monotherapy. In the USA, in less than 30% of hypertensives goal blood pressure is achieved. Combining drugs may help to increase the number of patients reaching goal. Combination therapy may also achieve other objectives:
   - improve patient compliance by a simple once-a-day regimen
   - reduce side effects
   - reduce cost

ii. There is large heterogeneity in response to drugs. Combining two different drugs from different classes with different mechanisms of action may address this problem.

iv. Use low-dose thiazide diuretics in most patients as part of the combination, as low-dose diuretics have proven themselves in many large trials.[2]

2. Stage two or higher hypertension:

Blood pressure > $^{160}/_{100}$ mmHg: initiate combination therapy, simply because it is less likely to respond to a single drug.

3. Proteinuria:

Systolic blood pressure must be reduced to < 125 mmHg, combination therapy will be necessary in most, if not all cases.

4. Diabetes mellitus:

SBP must be reduced < 130 mmHg. ACE-inhibitor/ARB is indicated, but not likely to succeed to reduce BP to goal as monotherapy.

5. Renal failure:

ACE-I/ARB will be part of it.[2]

Drug combinations in hypertension:

A. Diuretic: + Beta-blocker
+ ACE-inhibitor
+ ARB
+ Alpha-blocker

B. ACE-I/ARB: + Calcium antagonist (dihydropyridine; non-dihydropyridine).

C. Beta-blocker: + Calcium antagonist (only dihydropyridine)[4]

The value of combination therapy in hypertension:

A recently reported meta-analysis of 354 randomised trials published the following results:[5]

i. All five categories of drugs (diuretics, beta-blockers, ACE-inhibitors, angiotensin receptor blockers (ARB's), calcium channel blockers:

a. Produced similar reductions in blood pressure: average 9.1 mmHg reduction in systolic pressure, 5.5 mmHg in diastolic pressure when given in standard doses and only 20% lower at HALF standard dose.
b. The drugs reduced blood pressure from all pre-treatment levels (more so from higher levels).

ii. Combinations of drugs at HALF standard dose:

a. Blood pressure lowering effect of combinations was additive.
b. Prevalence of adverse effects with two drugs in combination at HALF standard dose were less than additive.
c. Adverse metabolic effects at HALF standard dose were negligible.

Conclusion:

Combination low dose drug treatment of hypertension increases efficacy and reduces adverse effects.

ALLHAT-trial:

The ALLHAT-trial, the largest ever randomised trial of antihypertensive treatment reaffirmed the use of combination therapy.[6] It confirmed the value of low-dose diuretics and, in this trial, to reach goal blood pressure of < $^{140}/_{90}$ mmHg, 63% of all participants needed a combination of drugs (two or more drugs). ALLHAT does not give information about the ideal combination of drugs required to achieve optimal blood pressure levels.

Recently the ASCOT-trial was stopped due to the superior efficacy of an ACE-inhibitor combined with a calcium antagonist, above the combination of a diuretic plus beta-blocker. These results have not been published yet.

References

1. Prospective studies collaboration. Age-specific relevance of usual BP to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002; 360:1103-1913.
2. JNC VII: JAMA 2003; 289:2560-2572.
3. Materson BJ. Combination therapy as the initial drug treatment for hypertension: when is it appropriate? AJ Hypertens 2001; 14:293-295.
4. Welsh L, Feno A. Drug treatment of essential hypertension: the case for initial combination therapy. Int J Clin Pract 2004; 58:956-963.
5. Law MR etal. Value of low dose combination treatment with blood pressure owing drugs. BMJ 2003; 326:1427-1431.
6. The ALLHAT Officers and Coordinators Collaborative Research Group. Effects of ACE-Is calcium antagonist and other blood pressure lowering drugs on mortality and major cardiovascular morbidity. Lancet 2002; 356:1955-1964.