Benefit and costs of anti-hypertensive treatment

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Hypertension is common throughout the world and represents the single greatest risk factor for increasing cardiovascular mortality, cardiovascular morbidity and overall mortality. Diseases associated with hypertension are not only, in general, of a chronic disabling nature, but, in most instances, require frequent hospitalization, with expensive drug treatment and management. Stroke, coronary heart disease, congestive heart failure and chronic renal insufficiency represent the most commonly encountered corollaries of inadequately treated hypertension. Anti-hypertensive treatment is accompanied by a reduction of hypertension-related cardiovascular risk and a clearcut benefit in terms of reduced incidence of major cardiovascular complications of hypertension and overall mortality. This benefit has frequently been underestimated in many clinical trials. Attempts to improve the cost–benefit ratio have included the use of treatment strategies based upon 24-h control of blood pressure, since it has been demonstrated that hypertension-related end-organ damage correlates more closely with 24-h average blood pressure and with 24-h blood pressure variability than with blood pressure measured in the clinic. It is hoped that new anti-hypertensive agents, which smoothly reduce 24-h blood pressure profile, will further reduce the incidence of hypertension-related end-organ damage.
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Hypertension as a health problem in the community

Hypertension is a major problem for the world population. Firstly, no single factor is more important for increasing cardiovascular mortality, cardiovascular morbidity and overall mortality than an elevated blood pressure[1]. Secondly, with the exception of a few ethnic groups of minuscule size[2], hypertension is common throughout the world, with a prevalence of 15–20% in adult and 30–40% in elderly age strata[1]. Thirdly, diseases associated with hypertension are mostly of a chronic, disabling nature. Furthermore, in most instances they require frequent hospitalization, with expensive drug treatment and management procedures. This is exemplified by stroke, for which hypertension represents the most important risk factor (followed by cigarette smoking)[1,3], together with coronary heart disease (CHD), congestive heart failure (CHF) and chronic renal insufficiency. CHD is three times more frequent in hypertensives than in normotensive individuals and the clinical manifestations of this condition (angina, myocardial infarction and sudden death) are no less dependent upon elevated blood pressure than upon elevated serum cholesterol (Table 1)[4]. Although not as important as it was 20 years ago, hypertension remains a common precursor and deter-minant (or co-determinant) of CHF[1,5]. Finally, an elevated blood pressure is, with diabetes, the major contributing factor for end-stage renal failure. In old age it can even be the only apparent determinant of this condition, being of greater relative importance than either diabetes or renal parenchymal disease[6,7].

Effect of anti-hypertensive treatment

Anti-hypertensive treatment is accompanied by a reduction of hypertension-related cardiovascular risk. Originally demonstrated for malignant hypertension[8], this has now been shown for virtually all types of hypertension, ranging across most spectra of severity and age[9,10]. The risk is also reduced when treatment is implemented in isolated systolic hypertension[11], whose prevalence shows a marked progressive increase above 70 years of age[12].

It has also been demonstrated that nearly all individual complications of hypertension are reduced by treatment. Thus, in patients with mild to severe hypertension, a 5–6 mmHg reduction of diastolic blood pressure is accompanied over a period of 5 years by a 40% reduction in the incidence of stroke[13]. Similarly, clinical manifestations of CHD are reduced by about 15%[13], whereas in both middle-aged and elderly hypertensive individuals a > 50% reduction in CHF is achieved by such a reduction in blood pressure[5]. There is also evidence (albeit less conclusive) that anti-hypertensive treatment favourably affects renal function and structure.

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Table 1   Increase in coronary heart mortality in relation to diastolic blood pressure and serum cholesterol values. Data from the MRFIT study. (Reproduced with permission from MRFIT Research Group[4])

	MRFIT						Framingham study†
	Special intervention			Usual care			
	Annual ECG only	Hospital Record only	Both	Annual ECG only	Hospital Record only	Both	
No. of events	75	123	96	82	158	83	72
Risk factors for non-fatal AMI (Cox multiple regression coefficients)							
Serum cholesterol (mg . dl⁻¹)	0·008*	0·005	0·007*	0·005	0·007†	0·011†	0·007†
Diastolic BP (mmHg)	0·013	−0·005	0·011	0·022	0·018	0·001	0·013
Smoking (no. cigarettes)	0·015*	0·009	0·019†	0·015*	0·015†	0·012	0·022†
Age (years)	0·024	0·035*	0·034	0·043*	0·018	0·010†	0·064†
CHD mortality in a subsequent year after non-fatal AMI	6·7%	4·2%	4·2%	9·8%	4·4%	1·2%	

The only non-fatal AMIs shown are those classified as 'definite' by one or both diagnostic approaches.
*$P<0.05$; †$P<0.01$ (these are the two-tailed probabilities that the coefficient is different from zero).
†Logistic regression coefficients for definite non-fatal AMI occurring during 8 years of follow-up for men in the Framingham cohort who were 35–57 at the outset. (Diastolic BP was not a significant risk variable for non-fatal AMI in this analysis but it was for CHD death both in Framingham and in MRFIT.)
AMI=acute myocardial infarction; BP=blood pressure; CHD=coronary heart disease; MRFIT=Multiple Risk Factor Intervention Trial.

This has been demonstrated by the fact that blood pressure reduction in patients with malignant hypertension prevents the development of renal failure, thereby removing a major cause of death in these patients[8]. Furthermore, the Hypertension Detection and Follow-up Program (HDFP) study demonstrated that a serum creatinine value $\geq 1\cdot7$ mg . dl⁻¹ occurred more frequently in patients in whom anti-hypertensive treatment was less aggressive (the referred-care group) as compared with patients in whom anti-hypertensive treatment was more aggressive (the special care group)[14]. Finally, evidence is available that a blood pressure reduction in hypertensive patients with diabetic nephropathy reduces micro-albuminuria, albuminuria and the rate of renal deterioration[15]. Although some anti-hypertensive drugs, such as angiotensin converting enzyme inhibitors, seem to be more effective than others, the associated nephro-protection is at least in part the result of the reduction in blood pressure. Indeed, even in normotensive subjects with diabetic nephropathy, a blood pressure reduction has been shown recently to be nephroprotective[16].

It may therefore be concluded that anti-hypertensive treatment is associated with a clearcut benefit and that the incidence of all major cardiovascular complications of hypertension is substantially reduced by such therapy. This leads to a reduction of all-cause death rate, as documented both by a meta-analysis of major intervention trials in hypertension[13] and by single intervention studies[17].

Cost-benefit ratio of anti-hypertensive treatment

Anti-hypertensive treatment is associated with a considerable cost, because anti-hypertensive drugs must be used in a large proportion of the population over a period of decades, since such agents do not remove the cause or causes of hypertension, but merely lower blood pressure on a day-to-day basis. Reducing the cost of treatment, however, is a difficult goal to achieve, because non-drug treatment of hypertension is effective in only a limited number of individuals[10,18,19]. Furthermore, some non-pharmacological approaches to the treatment of hypertension, such as dietary manipulation and physical exercise, may themselves be associated, either directly or indirectly, with considerable cost. Finally, some of these non-drug treatments are not devoid of side effects whose identification and correction has a financial counterpart. An example of this is a lower sodium diet which may lead, via sympathetic stimulation, to unfavourable modification of the patient's lipid profile. Indeed, one might take the paradoxical view that it might be desirable for the cost for anti-hypertensive treatment to increase, since some new, and more expensive, anti-hypertensive drugs have better safety and tolerance profiles than those of the traditional and less expensive anti-hypertensive agents, thereby reducing blood pressure with both fewer side effects and a better preservation of the quality of life[20]. Furthermore, and more importantly, because only 20% or less of hypertensive patients are effectively treated[21,22], it is frequently necessary to: (1) increase the use of anti-hypertensive drugs; (2) upgrade the frequency (and type) of blood pressure controls; (c) improve the quality of the patient–doctor relationship. In other words, a number of costly procedures may have to be implemented in an attempt to improve compliance with treatment.

It should be emphasized, however, that despite the high cost, the cost–benefit ratio of anti-hypertensive

treatment is favourable and that, in severely and/or elderly hypertensive individuals, its value is high[23]. It should also be pointed out that the benefit associated with anti-hypertensive therapy has been underestimated[24] for a variety of reasons. In many cases, calculation of benefit from anti-hypertensive therapy has been based upon clinical trials in which many patients underwent spontaneous blood pressure normalization, thus reducing the associated cardiovascular risk. In addition, many trials have had a high rate of crossover from the placebo to the active treatment group, thus blurring the differences between those receiving anti-hypertensive therapy and those on placebo. Furthermore, such trials have tended to last only 4–7 years, thereby missing the long-term advantages of anti-hypertensive treatment. These factors have combined to undervalue the ability of effective blood pressure control to prevent alterations of the cardiovascular system, such as arteriolar remodelling, cardiac hypertrophy and atherosclerosis, which lead to the clinical appearance of cardiovascular diseases years, or even decades later[25].

Increasing the cost-benefit ratio of anti-hypertensive treatment

Can the already favourable cost–benefit ratio of anti-hypertensive treatment be further improved? At present a major effort is being made to increase the benefit of treatment, because even in well-treated hypertensive patients, such as those in whom diastolic blood pressure is reduced to 90 mmHg, the cardiovascular risk remains much higher than that experienced by normotensive subjects[26,27]. The strategies currently being pursued to achieve this goal range from a better control of systolic blood pressure, including the reduction of diastolic blood pressure to values well below 90 mmHg, a greater attention to the cardiovascular risk factors frequently found in hypertensive patients and a wider use of anti-hypertensive drugs with properties that make them potentially capable of direct protection of the cardiovascular system and vital organ function. Also of current interest is a strategy based on a more accurate control of blood pressure throughout daily life, given the evidence that hypertension-related end-organ damage
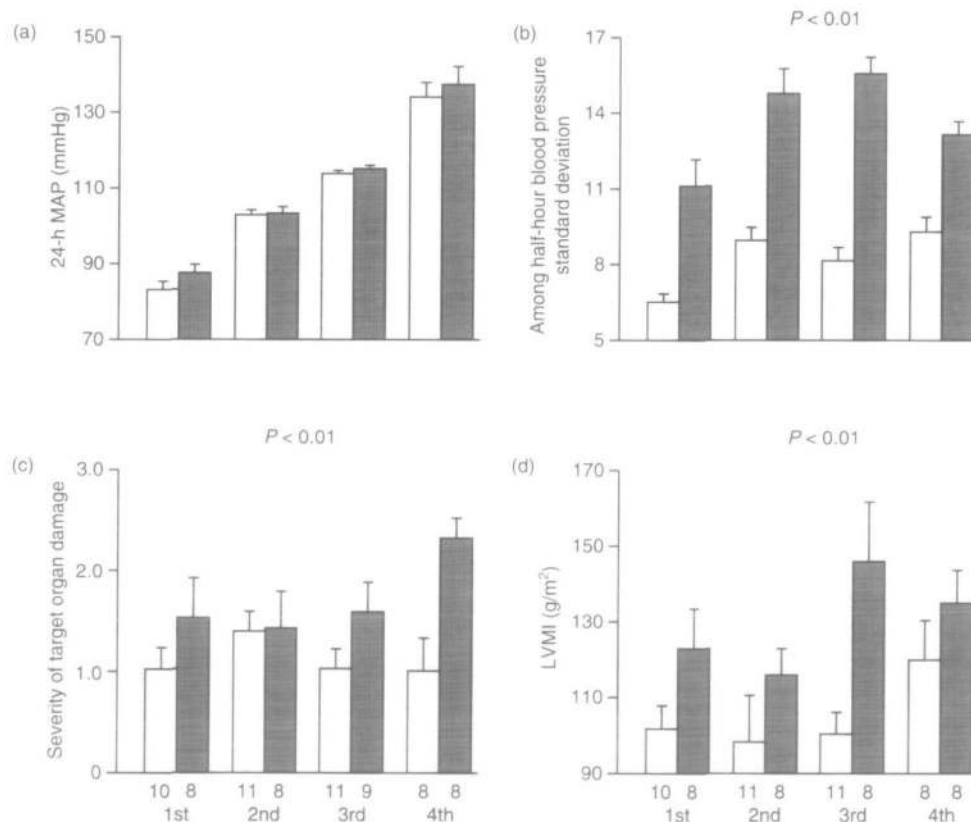
Figure 1 Data refer to hypertensive patients who were divided into four groups according to the 24-h mean blood pressure value (intra-arterial monitoring). Each group was subdivided into two classes according to the higher (■) or lower (□) value of 24-h blood pressure standard deviation. About 8 years later the patients having a greater standard deviation developed a greater score for end-organ damage and showed a greater left ventricular mass index (LVMI). (Reproduced with permission from Frattola *et al.*[29].)

correlates more closely with both 24-h average and 24-h blood pressure variability expressed as the standard deviation of the 24 mean h value (Fig. 1)[28,29] than with clinic blood pressure[30].

For the above reasons, new anti-hypertensive agents are currently evaluated not only for their ability to lower clinic blood pressure, but also for their ability to smoothly reduce the 24-h blood pressure profile. It is hoped that new anti-hypertensive agents, which can provide smooth and sustained 24-h blood pressure control, will further reduce the incidence of hypertension-related end-organ damage. The 24-h blood pressure profile is also frequently monitored in clinical practice before and during anti-hypertensive treatment. This is undertaken on the assumption that the higher cost of this procedure is more than neutralized by the identification of a number of subjects with a high clinic, but normal daily-life, blood pressure, in whom the cardiovascular risk is not elevated and treatment can thus be avoided or delayed. Furthermore, this approach may also be used for the purpose of titration of anti-hypertensive treatment to achieve optimal daily-life blood pressure control and thus more effective protection against the development of cardiovascular disease. Ongoing trials will show in the near future whether titration based on 24-h blood pressure variability correlates with a reduction in the incidence of cardiovascular disease and concomitant end-organ damage.

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