Systolic blood pressure and mortality

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Summary

Background The current systolic blood-pressure threshold for hypertension treatment is 140 mm Hg for all adults. WHO and the International Society of Hypertension have proposed that normal pressure be lower than 130 mm Hg, with an optimum pressure of less than 120 mm Hg. These recommendations are based largely on the assumption that cardiovascular and overall mortality depend in a strictly increasing manner on systolic blood pressure. The Framingham study was instrumental in establishing this viewpoint. We reassessed data from that study to find out whether the relation is strictly increasing or whether there is a threshold in this relation.

Methods We used logistic splines to model the relation of risk of cardiovascular and all-cause death with systolic blood pressure, using age-specific and sex-specific rates. We tested for the independence of the slope parameters from age and sex, and the reduced model with common slopes was used to produce a model different from the conventional linear logistic model.

Findings Against the predictions of the linear logistic model, neither all-cause nor cardiovascular deaths depended on systolic blood pressure in a strictly increasing manner. The linear logistic model was rejected by the Framingham data. Instead, risk was independent of systolic blood pressure for all pressures lower than a threshold at the 70th percentile for a person of a given age and sex. Risk sharply increased with pressure higher than the 80th percentile. Since systolic blood pressure steadily increases with age, the threshold increases with age, but more rapidly in women than in men.

Interpretation The Framingham data contradict the concept that lower pressures imply lower risk and the idea that 140 mm Hg is a useful cut-off value for hypertension for all adults. There is an age-dependent and sex-dependent threshold for hypertension. A substantial proportion of the population who would currently be thought to be at increased risk are, therefore, at no increased risk.

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Introduction

Current medical treatment of hypertension in adults aims to lower systolic blood pressure, for all ages and both sexes, to a resting value lower than 140 mm Hg. This threshold, which is partly arbitrary, is used to define hypertension. The sixth report of the Joint National Committee on the Detection, Evaluation, and Treatment of Hypertension (JNC/6) recommends that normal systolic pressure is less than 130 mm Hg and that an optimum pressure is less than 120 mm Hg.[1] Such an aggressive approach to hypertension is based on the general belief that there is a strictly increasing relation between systolic blood pressure and cardiac risk. For example, JNC/6 states, "This relationship is strong, continuous, graded, consistent, and etiologically significant".[1] WHO and the International Society of Hypertension (ISH) have also adopted the JNC/6 recommendations.[2] Since at least 50% of the population have systolic blood pressures between 120 mm Hg and 140 mm Hg, these new standards have generated some concerns.[3]

The concept that lower blood pressure implies lower risk is derived mainly from the use of linear logistic regression to model the relation. Generally, it is believed that this is the only simple model that is consistent with the data from epidemiological studies. Keys[4] investigated the relation of overall death and coronary-heart-disease death with systolic blood pressure in men. By simple graphical analysis of the raw data, he saw that the risk of death was apparently constant for all men with systolic pressures in the lower 70% for their age; the risk increased sharply for those with pressures in the upper 20% for their age. Based on his analysis, Keys concluded that the relation is non-linear and, therefore, the assumption of a simple linear relation and the use of the linear logistic model are unjustified.

The Framingham study[5] was instrumental in establishing the current viewpoint. We reassessed the Framingham 18-year data on the relation between systolic blood pressure and the hard endpoints of all-cause and cardiovascular-disease death. We focused especially on all-cause death for two reasons: it is the most free of misclassifications and, importantly, the number of events is sufficiently high to allow accurate estimates of the shape of the relation with systolic blood pressure. We chose the Framingham study because it was large, carefully done, is widely cited, and is one of the most influential studies leading to the current viewpoint; it included women and older people; and at the 18-year point the study was little affected by antihypertensive drug intervention.

Methods

The Framingham data are presented separately for three age-groups for each sex: 45–54 years, 55–64 years, and 65–74 years. Since age and sex are risk factors for mortality, especially cardiovascular death, and since systolic blood pressure increases continuously with age, the effects of sex and age need to be from that of systolic blood pressure on mortality. We therefore did separate analyses using the distinct groups rather than using a single adjusted rate.

Percentage group	Men			Women		
	Pressure (mm Hg) at 45–54 years	Pressure (mm Hg) at 55–64 years	Pressure (mm Hg) at 65–74 years	Pressure (mm Hg) at 45–54 years	Pressure (mm Hg) at 55–64 years	Pressure (mm Hg) at 65–74 years
10%	111	112	119	110	116	123
20%	117	120	127	116	124	130
30%	122	126	133	121	131	140
40%	127	131	139	126	137	147
50%	131	136	146	131	142	153
60%	136	142	152	136	151	160
70%	141	148	159	142	158	167
80%	148	158	169	151	168	177
90%	159	173	184	165	183	190

Table 1: **Decile values for statistic blood pressure by age group and sex**

Keys' results[4] suggest that mortality remains constant to at least the 70th percentile of systolic pressure for a man of a given age and rises for pressures higher than the 80th percentile. We first used Keys' heuristic graphical procedure to see if this hypothesis applied to the Framingham data. For each age-group of men, mortality risk was determined for each of the ten decile classes (table 1) and then these risks were pooled by decile class to give an overall picture of the relation of risk of death as a function of systolic pressure.

The first step in the formal statistical analysis was to find out whether there was a linear logistic relation between death rate and systolic blood pressure to the 70th percentile. This was done in two ways. First, we fitted separate linear logistic curves to death rates to the 70th percentile pressure for each group and tested to see if these slopes are all zero. Second, we fitted linear logistic curves having a common slope to the six groups and tested to see if that slope is zero.

We used logistic splines to model the relation between death and systolic blood pressure and to find out whether the linear logistic model is valid. A logistic-spline curve consists of two logistic curves (a left and a right) joined continuously at a point called the knot. Such a curve has four parameters: an intercept term, a left slope, a right slope, and the knot. In all our models, the knot was specified in advance and was therefore not an unknown parameter. There are two special cases of the logistic-spline curve of particular interest. The horizontal logistic-spline curve is the special case when the left slope is constrained to be zero; the ordinary linear logistic curve is the special case when the left and right slopes are the same. The logistic-spline model consisted of six logistic-spline curves, one for each of the six groups. The horizontal logistic-spline model was the sub-model in which the six logistic splines were horizontal logistic splines, and the linear logistic model was the sub-model in which the logistic splines were linear logistic curves. The linear logistic model and the horizontal-spline model had the same number of unknown parameters and were, therefore, equally simple models.
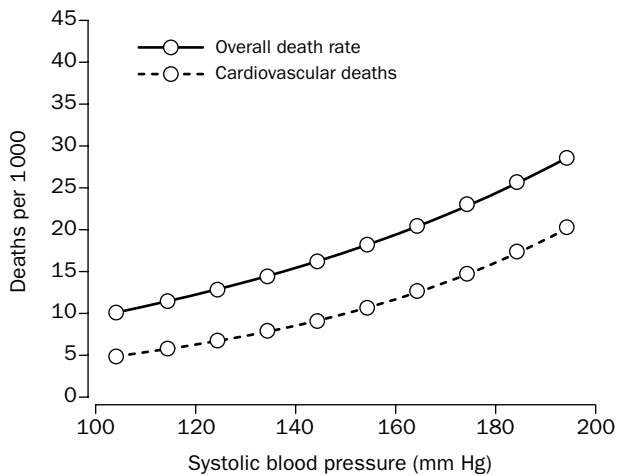
The reduced logistic-spline model was the logistic-spline model constrained to have a common left slope and a common right slope. The reduced horizontal-spline model was the horizontal-spline model with all the left slopes as zero and the reduced logistic model was the logistic model with the six curves constrained to have a common slope.

Keys' results suggest that the threshold is between the 70th and 80th percentiles of systolic blood pressure. In all our models, the knot was chosen to be the 70th percentile for each group. This produced a model that was as close as possible to the linear logistic model and that still allowed for flatness in the early part of the relation. We first fitted the logistic-spline model and tested to see if all the left slopes were the same and if all the right slopes were the same. We then fitted the reduced logistic-spline model and used the estimates of the left and right slopes to find out whether they were significantly different and to see if the left slope was significantly different from zero. To show that the linear logistic model does not hold, it is sufficient to show that there is some choice of the knot in the reduced logistic-spline model such that the left and right slopes are significantly different. Finally, as an alternative to the linear logistic model, we fitted the reduced horizontal-spline model with knot at the 70th percentile for each group.

Details of the statistical analyses are available from the authors.

Results

One of the most widely cited of the Framingham results is their age-adjusted and sex-adjusted death rate as a function of systolic blood pressure (figure 1), which suggests a "continuous graded" relation. However, their adjusted rate is not determined by one of the usual methods. Instead, it is a smoothed rate produced by use of linear logistic regression. For comparison, figure 2 shows the direct age-adjusted rate. Framingham's method necessarily removes any flatness in the data. Their finding of a strictly increasing relation may, therefore, be simply an artefact of the linear logistic model.
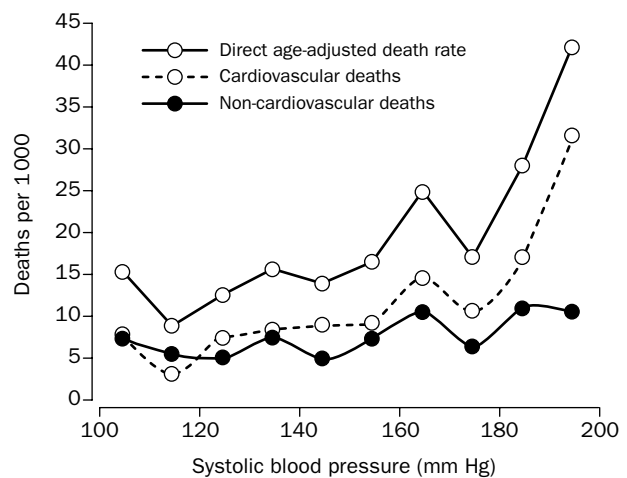

Figure 1: **Framingham age-adjusted rates for men aged 45–74 years related to systolic blood pressure**

Smoothed rates obtained by linear logistic regression. Marked points are computations reported in Framingham study. Note the suggestion of a strictly increasing relation.

Figure 2: **Actual age-adjusted rates for men aged 45–74 years related to systolic blood pressure**

Based on age-specific rates in Framingham study. The direct age-adjusted rate is the sum of the lower two curves.

Analysis of the pooled data for men strongly suggested that the risk of death was independent of percentile of systolic pressure up to at least the 70th percentile. Risk sharply increased after the 80th percentile (figure 3). Therefore, the Framingham data for men agree with Keys' findings. For this purpose we used the age-specific distributions of systolic blood pressure from the Framingham cohort, which agreed closely with those from the National Health Survey.[6]

Tests for trend to the 70th percentile pressure showed there was none (p=0·77 for separate slopes and p=0·69 for common slopes). The simultaneous test for equality of all left slopes and equality of all right slopes showed that there is no reason to doubt these assumptions (p=0·84). In the reduced model, estimates of the left and right slopes together with their SE showed that there was a significant difference between them (p=0·001), with the right slope being 10·8 times larger than the left slope. This finding shows that the linear logistic model is rejected by the Framingham data. The left slope in the reduced model was not significantly different from zero (p=0·49) and, therefore, there was no evidence against the reduced horizontal-spline model.

Our alternate model for the relation between death and systolic blood pressure was the reduced horizontal logistic-spline model, with thresholds at the 70th percentile pressure for each of the six groups. Risk of death had the same dependence on percentile of pressure in each of the six groups—namely, risks are constant to 70th percentile and then rise. However, since the 70th percentile pressure was dependent on age and sex when we look at the relation directly in terms of systolic
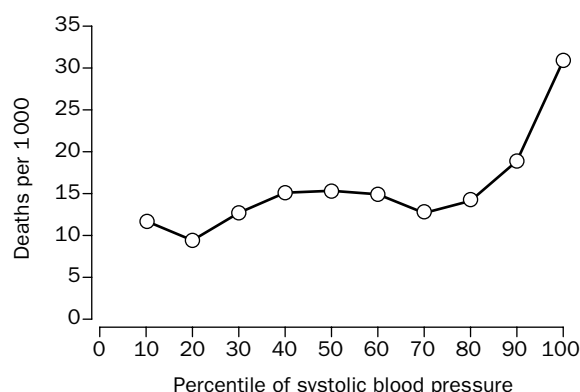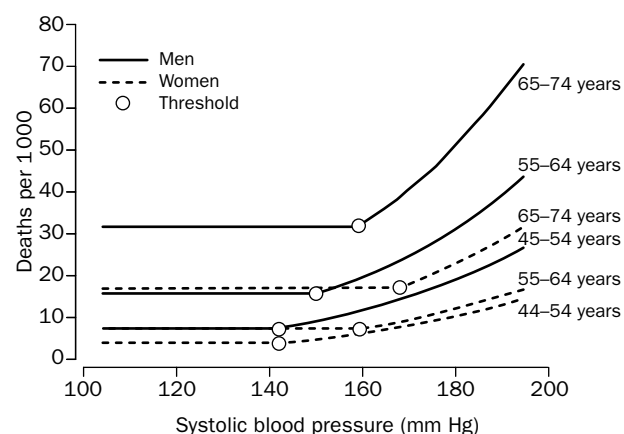
pressure, the constant portion extended further to the right with increasing age (figure 4). As judged by the goodness-of-fit test, the model gave an excellent fit to the data (p=0·47). The model is robust for location of the knot, since a small change (about 5 mm Hg) in its location produced only a small change in the accuracy of the fit. A comparison of the reduced horizontal spline model with the reduced linear logistic model showed that the latter model greatly overestimated the risk for more than 70% of the population (figures 5 and 6).

The horizontal spline model had a common slope for the six groups. A test of the accuracy of the model is to estimate this slope with data only from the women and use this estimate to predict the rate in men or the other way around. These predictions were accurate. The predicted death rates for each sex were essentially as good as the fitted rates.

The same analysis of death due to cardiovascular disease also showed that the reduced linear logistic model was rejected and the horizontal logistic spline model represented the relation accurately.

Discussion

Contrary to widely cited interpretations, reanalysis of the Framingham 18-year data showed that the relation between systolic blood pressure and all-cause and cardiovascular mortality is not strictly increasing. The linear logistic model used to generate that relation was rejected by the Framingham data. Instead, risk is unrelated to systolic pressure to at least the 70th percentile for each age and sex, and sharply increases with blood pressure higher than the 80th percentile. Our new (reduced horizontal-logistic spline) model represents this behaviour by putting a threshold at the 70th percentile, with risks constant for pressures lower than this threshold, then increasing logistically for pressures higher than the threshold (figure 4). Since systolic blood pressure steadily increases with age, but at different rates in men and women, the threshold is age and sex dependent.

The model is not critically dependent on the precise location of the threshold, which can be moved about 5 mm Hg to the right or left with little effect on the accuracy of the model. This latitude allows rules of thumb for the threshold for a person of a given age and sex: threshold=110+(2/3)(age) for men and threshold= 104+(5/6)(age) for women.

Figure 3: **Overall risk by percentile**
Pooled death rates by percentile class for men aged 45–74 years.

Flgure 4: **Reduced horizontal-logistic-spline fits**
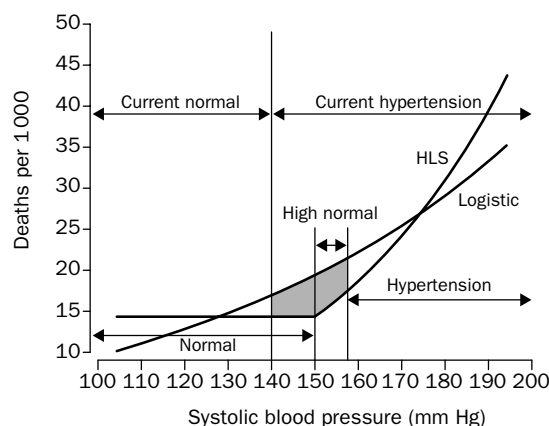

Figure 5: **Comparison of horizontal-logistic-spline and linear-logistic models**
Curves are for age-group 55–64 years. Shaded area represents individuals (about 30% of this population) may not require treatment.
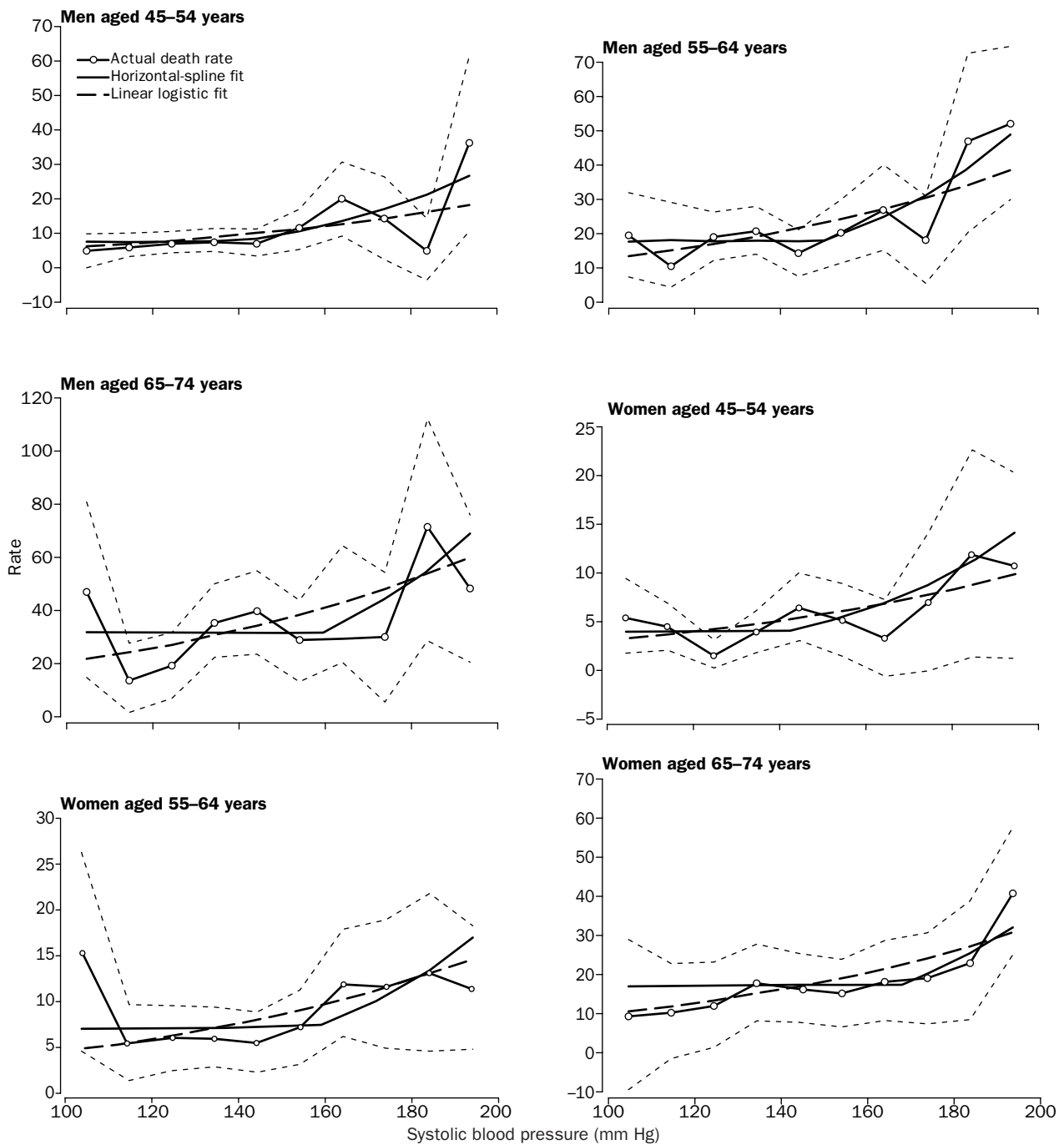
Figure 6: **Reduced horizontal-spline and linear logistic models and actual death rates (95% CI) for each group**

Our new model shows that there is an age-dependent and sex-dependent background risk of death that is independent of systolic blood pressure. Systolic pressure increases risk to higher than these background levels, but only for pressures that exceed a sex-dependent threshold, which advances with age. The rules of thumb show: an older person can have a higher systolic pressure than a younger person with no increased risk; a woman of a specified age older than 36 years can have a higher systolic pressure than can a man of the same age, with no increased risk. The increase in the odds ratio of death, for a specified increase in systolic blood pressure higher than the threshold, is the same for all ages and both sexes.

Clearly, the new model shows that the current cut-off value of 140 mm Hg for systolic hypertension for all adults is unjustified, since the value should be age and sex dependent. Indeed, even from the traditional viewpoint, this threshold for hypertension has been criticised for ignoring age dependence.[7] More importantly, the current viewpoint, based on the linear logistic model, denies even the concept of a normal systolic pressure, because in that model, risk necessarily increases smoothly with pressure. It takes the 140 mm Hg cut-off value to be essentially arbitrary (and perhaps too high[1,2]) with no real intrinsic justification.

By contrast, our new model suggests that there are natural cut-off values for hypertension, and that there is real meaning to normal compared with raised systolic blood pressure. One possible cut-off point is the threshold pressure. This may, however, be too conservative. The

Category	Increase above background	Range
Normal	None	Systolic pressure <70th percentile
High normal	Slight	Systolic pressure between 70th and 80th percentiles
Hypertension	Rapidly increasing	Systolic pressure <80th percentile

Table 2: **Risk classification by systolic blood pressure**

sharp change at the threshold is an artefact of the model. We know that risk is constant to at least the 70th percentile of systolic blood pressure and increases beyond the 80th. What really happens between the 70th and 80th percentile is that risk begins to increase to higher than background levels, but at an indeterminate point. The constancy could extend up to the 80th percentile. Hence, risk may not exceed background levels until the 80th percentile. Therefore, if the hypertension cut-off point is taken to be the point at which intervention is advisable, use of the 80th percentile seems warranted. Since the 80th percentile is about 10 mm Hg higher than the 70th, the previous rules of thumb show that the cut-off value for hypertension should be 120+(2/3)(age) for men and 114 (5/6)(age) for women. Our model suggests a new classification for risk by systolic pressure (table 2).

Comparison of the conventional linear logistic model with our new model (figure 3) shows that the linear logistic model underestimates the risk in the lower blood pressure range (<130 mm Hg) and in the higher blood pressure range (>170 mm Hg). More seriously, however, that model substantially overestimates the risks in the mid-range of pressures (about 130–170 mm Hg). Most individuals have pressures in that mid-range, and the current clinical guideline of 140 mm Hg lies towards its lower end. Consequently, a substantial number of people who have no increased risk may receive treatment, especially the elderly. By actual numbers, the percentage of men who have systolic blood pressure between 140 mm Hg and the 70th percentile pressure is 2% at age 45–54 years, 20% at age 55–64 years, and 22% at age 65–74 years. For women these percentages are 3%, 24%, and 40%, respectively. An additional 10% fall between 140 mm Hg and the 80th percentile pressure.

There is a widespread misconception that clinical intervention trials have shown that systolic blood pressure reduction confers benefit for mortality and cardiovascular disease, even for systolic blood pressure higher than 140 mm Hg but lower than the risk threshold (70th percentile) we identified. However, a review of the trial results shows that they support, rather than conflict with, our analysis.

First, despite the popular belief to the contrary, no prospective, randomised, placebo-controlled clinical trial shows significant survival benefit for people starting with systolic blood pressures between 140 mm Hg and 160 mm Hg, where we identified the risk thresholds. Second, most trials relating blood pressure to mortality are based on diastolic, not systolic pressure. Third, many clinical trials draw conclusions and make recommendations about the lower range of systolic blood pressures based on extrapolation requiring the incorrect assumption that the linear logistic model is valid. Last, most of the clinical trials combine all participants with systolic blood pressure higher than 140 mm Hg, which includes people with pressures lower than and higher than the 70th percentile risk threshold. Thus, any benefit from decreasing systolic blood pressure for the group could be attributable to people whose pressures started above the risk threshold, who are expected to benefit.

Perhaps the most frequently cited trial on the relation of systolic pressure to mortality is the Systolic Hypertension in the Elderly Program (SHEP),[8,9] which focused on systolic blood pressures higher than 160 mm Hg in people older than 60 years. Since the goal in that study was to decrease systolic blood pressure to lower than 160 mm Hg, it sheds no light on the linearity of the relation or of benefit for those below the threshold for risk.

Most importantly, whenever a treatment is used to treat a surrogate endpoint (such as systolic blood pressure) for a target outcome (such as mortality), and the drug affects other parameters, confounding can occur. The possibility that the treatment acts directly on the target must be excluded, with the effect on the surrogate being an irrelevant side-effect. Antihypertensive agents have potent effects on the cardiovascular system, which could explain any benefit derived from the drug, independent of the effect on blood pressure.

One way to disentangle the confounding is to assess whether antihypertensive agents that have similar effects on systolic blood pressure have the same or different effects on outcomes. For example, Psaty and colleagues[10] have shown that low-dose diuretics, high-dose diuretics, and β-blockers all lower blood pressure by about the same amount, but effects on outcome differed significantly. Another way to disentangle the confounding is to assess whether drug action benefits survival independently of systolic blood pressure. Borghi and Ambrosioni[11] reported a protective role for inhibitors of angiotensin-converting enzyme, even in hypertensive diabetic patients. They noted that such agents can significantly decrease the occurrence of major cardiovascular events (coronary heart disease and stroke) largely independent of blood pressure control, an effect not seen with the use of calcium antagonists. The beneficial effects of β-blockers, independent of blood pressure, include protective effects against arrhythmias, ischaemia, and atherosclerosis. Many other studies show that antihypertensive agents favourably affect many cardiovascular parameters, including survival, but that their effects on systolic blood pressure may be of no consequence.

Our results do not diminish the importance of antihypertensive treatment. These drugs can clearly lower various risks. Our results do, however, show that treatment based solely on systolic blood pressure exceeding 140 mm Hg is not justified.

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Cost-effectiveness of public-funded options for cataract surgery in Mysore, India

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Summary

Background In India 3·8 million people become blind due to cataracts every year. We assessed the cost-effectiveness of public-funded options for delivering cataract surgery in Mysore, Karnataka State, India.

Methods Three types of delivery of cataract surgery were studied: mobile government camps, walk-in services at a state medical college hospital, and patients transported in from satellite clinics to a non-governmental hospital. We assessed outcomes in a systematic sample of patients operated on in 1996–97 by follow-up at home; average costs by provider derived from actual expenditures during the year.

Findings Almost half the patients operated on in government camps were dissatisfied with the outcome (34/70, 49% [95% CI 36–61]). More than one third were blind in the operated eye (25/70, 36% [25–48]). User satisfaction was higher with other providers (medical college hospital 82% [63–94]; non-government hospital 85% [72–93]), and fewer patients remained blind. Camps were a low-cost option, but the poor outcomes reduced their cost-effectiveness to US$97 per patient. The state medical college hospital was least cost-effective, at US$176 per patient, and the non-governmental hospital was the most cost-effective at US$54 per patient.

Interpretation The government of India should review its policy for government camp surgery, and consider alternatives, such as transporting patients to better permanent facilities. India and other developing countries should monitor outcomes in cataract surgery programmes, as well as throughput.

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Introduction

The 8·9 million blind people in India account for 24% of blindness worldwide, and increased life-expectancy in the country means 3·8 million people become blind due to cataracts every year.[1,2] The National Blindness Control Programme started in 1976, but technical, logistical, and funding problems impaired its effectiveness. The Indian government renewed efforts in 1993–94 with a US$118 million World Bank credit. As cataracts cause 50–80% of the blindness,[3,4] the government aimed to expand cataract-surgery coverage to the disadvantaged, and improve its quality, and thus reduce the prevalence of blindness.[5] Funds are now allocated to District Blindness Control Societies, which are autonomous legal entities at the district level. These societies have the flexibility to finance different providers, and therefore influence the mix of services available to low-income groups.

Mobile camps are an important component of these services for people in rural areas, where surgical teams establish temporary operating services in improvised facilities. They are considered to be cheap, efficient, and accessible to the rural poor. Societies also provide funds to non-governmental providers for cataract surgery.

Total national cataract throughput has increased from 1·2 million in 1991–92 to about 2·7 million cataract operations in 1996–97,[6] but little is known about comparative cost-effectiveness of the various providers. We therefore compared the outcomes, costs, and cost-effectiveness of the three most widely used public-funded strategies for the provision of cataract surgery in one district in Karnataka.

Patients and methods

Patients

Karnataka State is in the south-west of India, has a population of 45 million (1991 national census), and for selected indicators of social health, ranks high nationally. The Danish Government are helping implement the Karnataka project; in the seven other Indian states supported by the World Bank, the government is managing project implementation. We selected Karnataka because it was one of the first to establish blindness-control societies, and because the project is widely regarded as a model example of the National Blindness Control Programme.

Out of a total of 19 districts, we identified six that achieved 80–100% cataract-surgery targets in 1996–97. Of these six districts, we selected one at random for study, which was Mysore. In this location, the programme supported: the state medical