Hotline Editorials

There is a non-linear relationship between mortality and blood pressure

'*For every complicated problem there is a solution that is simple, direct, understandable, and wrong*' — H. L. Mencken

Background

Stamler[1] stated 'the relation of SBP [systolic blood pressure] to risk of death is continuous, graded, and strong, and there is no evidence of a threshold . . .'. The formulation of this 'lower the better' principle, in terms of the linear logistic model (often referred to simply as the linear model) is the paradigm for the relationship of all cardiovascular risks to blood pressure and forms the foundation for the current guidelines for hypertension[2,3].

But it is often forgotten that when a study reports a linear (or any other) relationship between two variables it is not the data itself, but the model used to interpret the data, that is yielding the relationship. Almost universally, studies that report a linear relationship of risk to blood pressure, do so via the linear models such as the Cox model or the linear logistic model. Formally, that model can be applied to any bivariate data and, independently of the data, will always show that there is a linear relationship between the two variables. Before one can have confidence that the stated linearity correctly reflects the behaviour of the data, and is not just an artifact of the model, it is necessary to carefully examine the data in relation to the proposed model. At a minimum, it must be demonstrated that the model actually 'fits' the data and that it does not 'smooth away' important features of the data.

Twenty years ago Keys[4], using simple graphical methods, concluded that the linear model, in terms of the relationship of overall and coronary heart disease death to blood pressure was unjustified. Could Keys be correct? To see, we reexamined data from the Framingham Heart Study[5,6]. That carefully conducted and most widely cited study played a seminal role in firmly entrenching the current linear thinking on blood pressure. Although 'soft' end-points, such as cardiovascular risk, are certainly of interest, they lack the statistical reliability of the 'hard' end-points of overall and cardiovascular mortality. Therefore, to minimize extraneous statistical issues, our first reevaluations were limited to the hard end-points of overall and cardiovascular death. By 18 years of follow-up, the increasing use of antihypertensive medication was starting to have appreciable effects on the distribution of blood pressure in the Framingham cohort[7]. Therefore, we limited our analysis to the 18-year follow-up data. The use of the full (34 year) data would have introduced serious confounding in the natural relationship of cardiovascular risk to blood pressure, which was our primary interest.

The paradigm is false

Shockingly, we have found that the Framingham data in no way supported the current paradigm to which they gave birth[5]. In fact, these data actually *statistically rejected the linear model*. This fact has major consequences. Statistical theory now tells us that *the paradigm MUST be false for the target population of the study* (white, urban middle class Americans ages 45–74). Consequently, provided that the study itself has no serious flaws, there are only three possibilities for any other study that fails to reject the linear model:

(1) It lacks sufficient statistical power to detect that linearity is false (e.g. it is too small).
(2) It is a sample from a population that differs significantly from the Framingham target population.
(3) It is seriously biased.

New model for the risk — systolic blood pressure relationship

Systolic blood pressure increases at a constant rate with age[7]. In sharp contrast to the current paradigm, we find that this increase does not incur additional risk. More specifically, all persons in the lower 70% of pressures for their age and sex have equivalent risk.

However, risk rapidly increases with pressure for those in the upper 20% of pressures for their age and sex.

We introduced a new model for the relationship of the risk of overall or cardiovascular death to systolic blood pressure that incorporates these observations.[5] The salient features of the new model are:

(1) There is an age- and sex-dependent background risk that is independent of systolic blood pressure.

(2) In contrast to the current paradigm, there is an age- and sex-dependent threshold; risk only increases steadily with pressures that exceed that threshold.

(3) The threshold keeps pace with the increase in pressure with age; it always can be taken to be the 70th percentile of systolic blood pressure for a person of a given age and sex. The rule of thumb is that it is at 110+(2/3) (age) for a man 45–74 and 104+(5/6) (age) for a woman 45–74.

(4) Although the point at which the increase in risk begins depends on age and sex, the relative risks for pressures above threshold are the same for all ages and both sexes.

The following facts should be kept in mind in interpreting the model. The precise location of the threshold is essentially indeterminate. Somewhere between the 70th and 80th percentile risk begins to smoothly increase above background, but there is probably no well-defined point at which that occurs. We simplify the picture by fixing the threshold at its lowest possible value. This produces a conservative model that underestimates the threshold location. It also produces an artifact of the model with an apparent sharp change at the threshold. The model is robust with respect to the location of the threshold in that any choice of threshold between the 70th and 80th percentile produces models of about the same accuracy.

Clinical implications of the new model

According to the current paradigm, there is no normal systolic blood pressure except by convention. Somewhat arbitrarily, for every adult, the cut-point for hypertension is set at 140 mmHg. However, the Sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC-VI) and the joint report of the World Health Organization and International Society for Hypertension (WHO/ISH)[2], clearly motivated by the current paradigm, believe that may be too high. They suggest that 130 mmHg be the cut-point for 'normal' with 120 mmHg being
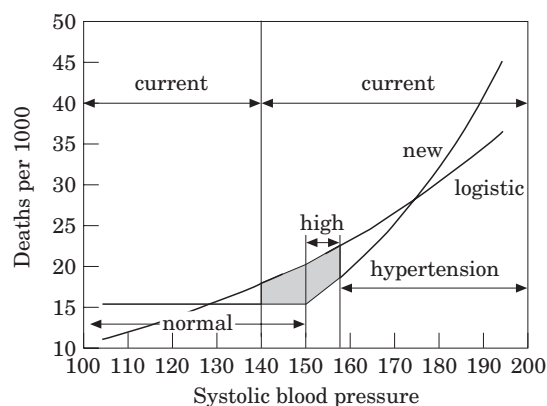
Figure 1 **Comparison of the two models ages 56–64. The shaded area represents the individuals (about 30% of this population) who may be inappropriately treated by the present criterion.**

'optimal'. The invariance of the hypertension cut-point with age and sex combine with the rise in systolic blood pressure with age to automatically put an ever increasing portion of the ageing population in the hypertensive category who are therefore to be considered in need of (mostly pharmacological) intervention.

Our findings show there is no increase in risk with the nominal increase in systolic blood pressure with age. In place of a fixed pressure set by convention, we find there are natural candidates for hypertension cut-points that are based on a fixed percentile of pressure rather than a fixed pressure. Consequently, a universal cut point at a fixed pressure, in particular at 140 mmHg, has no justification; the cut-point for hypertension in terms of systolic blood pressure itself must be age- and sex-dependent.

The two obvious choices for a hypertension cut-point are the points where constancy ends and where increased risk definitely begins. The former leads to the 70th percentile as the cut-point and the latter to the 80th percentile. The 70th percentile is a very conservative cut-point. The 80th percentile, though less conservative, leads to a point where intervention is warranted. In the spirit of the current guidelines classification our new model suggests the following reclassification: normal systolic blood pressure — less than the 70th percentile, high normal — between the 70th and 80th percentile, hypertension — greater than the 80th percentile.

Comparing the current linear model and our new model shows the following: (see Fig. 1)

(1) The logistic model under-estimates the risk for those with systolic blood pressure currently considered optimal (because it claims they have less risk than the background risk). This defect is of little consequence.

		Men			Women	
Age (years)	45–54	55–64	65–74	45–54	55–64	65–74
70th percentile	2	20	22	3	24	40
80th percentile	12	30	32	13	34	50

(2) More seriously, the linear model considerably under-estimates the risk for systolic blood pressure above the 80th percentile. Risk rises substantially more rapidly for persons in the upper 20% of pressures for their age and sex with the new model than with the current linear model. Thus, these persons may require more aggressive therapy than was previously believed.

(3) Most importantly, the current paradigm considerably over-estimates the risk in the mid-range of pressure (roughly 125–180 mmHg). This has major consequences. The vast majority of the population falls into that mid-range and the cut-point of 140 mmHg lies towards its lower end. Consequently, a large proportion of the population considered at increased risk with the current 140 mmHg cut-point are in fact at no increased risk (see Table 1).

Clinical trials

SHEP[8,9] is the trial most frequently cited as dealing directly with systolic blood pressure. That trial randomized persons 65+ with isolated systolic hypertension (systolic blood pressure between 160 and 204) into a treatment group (given drugs) and control group (given a placebo). All we know from that trial is that at the end there was a mean difference of 12 mmHg (155 vs 143) between the control and the treatment groups and a reduction in risk of certain outcomes. Nevertheless, Alderman[10] states, '. . . according to the Port logic, treatment might have stopped at 155 mmHg instead of 143, and therefore, the important benefit of a lower pressure would have been missed'. This is not a valid deduction from SHEP. There is no way one can determine which individuals gained the benefit or contributed to the difference between the means. Was it those who had pressure reduced from 160 mmHg to 140 mmHg or from 180 mmHg to 160 mmHg that gained the benefit? Alderman, thinking linearly, falsely assigns it to those reduced to the lowest values. While our model shows that there would be no benefit in reducing pressure from 160 mmHg to 140 mmHg it does show there could be substantial benefit in reduc-

tions from 180 to 160 mmHg. In sum, SHEP cannot discriminate, for any outcome, between our proposed model and the linear model.

More generally, *no randomized trial has ever demonstrated any reduction of the risk of either overall or cardiovascular death by reducing systolic blood pressure from our thresholds to below 140 mmHg*.

It is widely believed that randomized trials have proved that lowering blood pressure is beneficial. Actually, that is not true. All antihypertensive drugs have profound effects on the cardiovascular system, aside from their haemodynamic effect. How much, if any, of the observed risk reductionship can be ascribed to the reduction in pressure and how much to the direct action of the drug on the cardiovascular system? Motivated by the belief in the linear relationship of risk to pressure, many automatically attribute the risk reduction to the pressure reduction, ignoring the direct action of the drugs on the target outcomes. But, results of a multitude of clinical trials make it clear that such a simplistic view cannot be true. In fact, evidence is mounting (especially from the newer trials) that it is the direct effects that are producing most, if not all, of the benefit and that the accompanying blood pressure reduction may be just an inconsequential side effect. As examples, consider:

- The direct benefits of beta-blockers and diuretics have been known for some time.
- Drugs that lower blood pressure by about the same amount have very different effects on outcomes[11].
- Cardiovascular benefits of ACE inhibitors, independent of blood pressure, are not observed with calcium antagonists, despite the latter having more pronounced effects on blood pressure[12].
- HOPE[13–15] demonstrated that ACE inhibitors provided diverse and profound cardiovascular benefits, with only trivial differences in blood pressure between the treatment and control groups.
- ALLHAT[16] showed a dramatic difference in cardiovascular risk between alpha blockers and diuretics, with essentially no difference in their effect on blood pressure. The investigators of ALLHAT concluded, 'blood pressure reduction is an inadequate surrogate marker for health benefits in hypertension'.

Thus, while the randomized trials clearly show that some antihypertensive drugs can reduce various risks, none of them show that reducing blood pressure in and of itself has benefit. Our findings in no way challenge the conclusion that antihypertensive drugs can have pronounced benefits. However, they certainly show that the administration of these drugs, based solely on the fact that a person's systolic blood pressure exceeds 140 mmHg, cannot be justified.

Other studies

The counter arguments to our findings all centre on the alleged fact that other studies establish linearity. For example Levy[17] claimed that while he does not dispute our analysis as far as it goes, it ignores the 'mountain of other evidence' for the direct relationship between disease risk and blood pressure. Alderman[10] echoes such sentiments as well.

Let us consider the evidence from other studies. Do the other studies claiming linearity really support that claim? Prior to our reevaluation of the Framingham 18-year data, that study would certainly have been considered as giving evidence for linearity. Yet, under more careful scrutiny, linearity failed. Essentially all studies claiming linearity followed the Framingham model and used linear logistic smoothing. Consequently, the claims of linearity must now be seriously questioned; at this juncture we really do not know what these other studies actually show. All of them need to be reevaluated (perhaps with more powerful statistical procedures, as we used with Framingham).

Epilogue — diastolic pressure

The Framingham data show the paradigm of the relationship of cardiovascular risks to diastolic blood pressure is also false. We find that a model very similar to that with the systolic blood pressure prevails.

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