Review

The J-Curve Phenomenon and the Treatment of Hypertension

Is There a Point Beyond Which Pressure Reduction Is Dangerous?

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We critically appraised the medical literature to evaluate whether there is a point beyond which blood pressure reduction in hypertensive subjects is no longer beneficial and possibly even deleterious. Thirteen studies that stratified cardiovascular outcomes by level of achieved blood pressure in treated hypertensive subjects who had been followed up for at least 1 year were critiqued by four independent reviewers. Data addressing population, protocol, and methodological characteristics were evaluated. Studies did not show a consistent J-shaped relationship between treated blood pressure and stroke, but they did demonstrate a consistent J-shaped relationship for cardiac events and diastolic blood pressure. The beneficial therapeutic threshold point was 85 mm Hg. We conclude that low treated diastolic blood pressure levels, ie, below 85 mm Hg, are associated with increased risk of cardiac events.

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THERE is ample scientific evidence to conclude that uncontrolled hypertension increases cardiovascular morbidity and mortality, and clinical trial data have shown that lowering elevated blood pressure levels decreases morbidity and mortality. The question that remains is: "To what level should blood pressure be lowered to optimize treatment?" Recently, some authors have focused on the dangers of lowering blood pressure below certain levels and have suggested that excessive reductions in blood pressure may explain why major clinical trials have not shown greater effects in reducing coronary artery disease.[1-3] These authors have proposed a "J-shaped curve" relationship between blood pressure and cardiac morbidity and mortality, whereby lowering blood pressure below a critical point is no longer beneficial and possibly even deleterious. Other authors have maintained the traditional premise of "the lower the blood pressure the better."[4]

Support for the traditional therapeutic goal of "the lower the better" is based largely on the results of large observational studies and actuarial data. Although these studies often included normotensive subjects and stratified cardiovascular outcomes based on baseline rather than treated levels of blood pressure, they illustrate the controversy addressed in this review. For example, data from the massive Build and Blood Pressure Study,[5] the mortality surveillance study of the Multiple Risk Factor Intervention Trial screenees,[6] subsets of the Pooling Project,[7] the Framingham study,[8] and the Coronary Drug Project study,[9] as well as data from several lesser known studies,[10-15] have shown positive linear relationships without threshold points between baseline blood pressure levels and cardiovascular events. In general, these studies have analyzed data using best fit smooth curves between the points that relate blood pressure and cardiovascular events. These methods do not allow detection of a J-curve as to reveal a J-shaped curve individual points must be connected. Regardless of these limitations, the magnitude and consistency of these data have prompted many authorities to accept low blood pressure targets for hypertensive patients.

In fact, in a recent meta-analysis, MacMahon et al[4] combined nine observational studies and concluded that "there is no evidence of any threshold below which lower levels of blood pressure were not associated with lower levels of stroke and coronary heart disease." Their methods of analysis and results have been criticized.[16-18] The analysis was based on baseline rather than treated blood pressure levels, and five observational studies that did not support a continuous linear relationship were excluded.[19-28] Moreover, at

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least five population-based observational studies have shown increases in deaths at lower levels of diastolic blood pressure. Additional support for a J-shaped relationship comes from the reexamination by Anderson[24] of data from the Framingham study. Although these data initially seemed to support a linear relationship,[8] Anderson pointed out that the original data were logistically smoothed, and, therefore, the existence of a J-shaped relationship could be masked. He then reanalyzed the data and clearly showed an increase in cardiovascular events with diastolic blood pressure levels below 85 to 98 mm Hg.

In summary, large observational studies have been used to support the policy that blood pressure should be lowered as far as possible. The appropriateness of using these studies to set treatment goals for hypertensive patients is questionable, given their frequent inclusion of normotensive subjects, inappropriate analysis strategies, and classification of subjects based on baseline blood pressure levels only. In addition, reanalysis of data from the Framingham study, as well as original data from several European studies, has suggested that even in observational studies, the relationship between blood pressure and cardiovascular morbidity and mortality may not be linear. Hence, the specific question of this review is: "Is there a point beyond which blood pressure reduction in hypertensive subjects is no longer beneficial and possibly even deleterious?"

METHODS
Data Acquisition

A search of the English medical literature was performed using the MEDLINE on-line computer database for the years 1966 through 1989. Terms for the MEDLINE search included *hypertension, blood pressure,* and *morbidity and mortality.* Other sources of data included references identified from pertinent articles and written communications with international experts in the field of hypertension.

A total of 478 articles were identified from the MEDLINE database search. Of the 478 articles, 134 were deemed potentially relevant by two independent reviewers. "Potentially relevant" was interpreted broadly to include any study that correlated any blood pressure level with a cardiovascular or total mortality outcome. The methods sections of these 134 articles and a 10% random sample of the remaining 344 were reviewed by two reviewers to assess whether studies met four specific selection criteria. First, study populations had to involve hypertensive sub-

jects who were followed up for at least 1 year while undergoing antihypertensive treatment. Second, accepted outcomes included stroke and myocardial infarction incidence and total mortality and death due to stroke and cardiac events. Third, to detect a J-shaped relationship, outcomes had to be stratified by at least three treated blood pressure levels and had to include at least one level with achieved pressures of less than 90 mm Hg. Fourth, prospective or retrospective cohort and randomized trial designs were allowed.

Thirteen studies were identified that met selection criteria.[25-37] (None of these were identified from the random sample.) One other potentially relevant study[38] was cited by experts and article references, but published data from this study, which met selection criteria, were unavailable. The remaining 121 articles included 24 that provided duplicate and supplementary data for the 13 primary studies, one small study that had less than 1 year of follow-up, and 96 studies that failed multiple selection criteria. None of the excluded studies had outcomes presented by treated blood pressure levels (ie, all failed the third selection criteria).

Data Extraction

Articles were abstracted by four independent reviewers (L.F., C.D.M., W.D.L., and C.R.L.) using a standardized form. The form addressed subject population characteristics, study protocol characteristics, whether a J-shaped relationship was found and for what outcome measures, and eight items that were used to generate a quality score. Items rated for this score were (1) whether the study population was referred or community based, (2) whether outcomes were assessed in a "blinded" manner, (3) whether outcomes were assessed using an equal follow-up time (or adjusted for unequal follow-up times), (4) whether the percentage of the dropout rate was greater or less than 25%, (5) whether cointerventions were addressed, (6) whether results were adjusted for demographic factors (age and sex) and comorbid diseases or risk factors (preexisting ischemic disease, diabetes, hyperlipidemia, and smoking status), (7) whether precardiovascular event vs postcardiovascular event blood pressures were analyzed, and (8) whether statistical significance was evaluated. Scores could range from 0, indicating poor quality, to 15, indicating excellent quality. This quality score was weighted specifically to address methodological issues relevant to detect a J-shaped relationship. The scores do not necessarily reflect the

ability of studies to address their original hypotheses. The overall weighted κ value among the four assessors for these rankings was .62.

Data Synthesis

The data were reviewed qualitatively by specifically integrating study results with subject characteristics, study protocols, and study methods or quality. Quantitative estimates of the effects of treated diastolic blood pressures on ischemic heart disease events and mortality and total mortality were derived using least-squares regression models that weighted studies by person-years of observation.[39] (Longer studies with more patients received greater weights.) Models with higher-order polynomials were fit. Mallows C(P) statistic was used to determine the best fitting model.[39] The statistical significance of the model and its parameters were tested using F and t tests, respectively. Cerebrovascular events were not pooled because only three studies[26-28] gave these data separate from cardiac data, and one of these[27] was presented by changes in blood pressure rather than by treated level stratifications.

RESULTS
Subject and Protocol Characteristics

More than 48 000 subjects have been included in the 13 studies (Table 1). Approximately 54% have been men. Most subjects have been middle-aged, although some elderly subjects have been studied. No studies specifically excluded smokers or subjects with elevated cholesterol levels. Subjects often had known ischemic disease at entry, although four studies were designed to investigate patients who were relatively free of cardiovascular disease.[30,33-35] Most entry blood pressure levels have been in the mild to moderate range. One early, very small study (N = 58) dealt exclusively with severely hypertensive subjects; it is not presented in the tables or discussed further.[38]

Approximately half of the studies were designed as cohort studies and half as randomized trials. Average follow-up lengths varied from 4 to 12 years. Blood pressure measurements have been performed in the sitting position using phase V Korotkoff's sounds in all but one study.[30] Antihypertensive agents most commonly used were diuretics, β-blockers, or both, though some studies have included calcium channel blockers and angiotensin-converting enzyme inhibitors. Most studies have related achieved diastolic blood pressure levels to cardiovascular outcomes, though some have looked at achieved

Table 1.—Subject and Protocol Characteristics of Studies That Have Stratified Cardiovascular Outcomes by Levels of Achieved Blood Pressure*

Study	No. of Subjects	Mean Age, y	% Men	Mean Entry Diastolic BP, mm Hg	Includes Subjects With Cardiovascular Disease	Mean Follow-up Time, y	BP Phase	BP Position	Primary Drugs	Quality Score (0-15)
Cruickshank et al[25]	939	55	61	109	Yes	6.1	V	Sitting	AB, TD, PSD	5
DHCCP[26]	2145	51	50	107	Yes	4	V	Supine	Unclear	4
HDFP[27]	10 053	51	54	90-104	Yes	4	V	Sitting	AB, TD	8
Waller et al[28]	3350	50	50	110	Yes	6.5	V	Unclear	Unclear	5
HEP[29]	884	68	31	98	Yes	4.4	V	Sitting	AB, TD	4
Stewart[30]	169	44	71	124	No	6.25	IV	Unclear	AB, TD	7
NYEC[31]	1765	51	72	102	Yes	4.2	V	Sitting	AB, TD, CCB, ACE	11
EWPHE[32]	840	71	30	90-119	Yes	4.7	V	Sitting	TD, PSD	7
PPT[33]	686	52	100	106	No†	12	V	Sitting	AB, TD	14
IPPPSH[34]	6357	52	50	108	No	3-5	V	Sitting	AB, PSD	5
ANBP[35]	3931	50	55	101	No‡	4	V	Sitting	TD	4
MRC[36]	17 354	52	52	90-109	Yes	5.5	V	Sitting	AB, TD	6

*BP indicates blood pressure; DHCCP, Department of Health and Social Security Hypertension Care Computing Project; HDFP, Hypertension Detection and Follow-up Program; HEP, Hypertension in Elderly Patients; NYEC, the New York Employee Cohort Study; EWPHE, European Working Party on High Blood Pressure in the Elderly; PPT, Primary Prevention Trial; IPPPSH, International Prospective Primary Prevention Study in Hypertension; ANBP, Australian National Blood Pressure Study; MRC, Medical Research Council; AB, adrenergic blocker; TD, thiazide diuretic; CCB, calcium channel blocker; ACE, angiotensin-converting enzyme inhibitor; and PSD, potassium sparing diuretic.
†Excluded subjects with myocardial infarction or stroke within the past 2 years.
‡Excluded subjects with stroke and angina, as well as subjects with myocardial infarction within the past 3 months.

Table 2.—Summary of Findings for and Against a J-Curve Relationship for Various Cardiovascular End Points*

Study†	Stroke Incidence	Stroke Mortality	Myocardial Infarction Incidence	Myocardial Infarction Mortality	Total Mortality	Diastolic Blood Pressure J-Point, mm Hg
Cruickshank et al[25]	...	PRO¶	...	PRO	CON	85-90
DHCCP[26]	...	CON	...	PRO	CON	86-91
HDFP[27]	...	...	...	...	PRO	26#
Waller et al[28]	...	CON	...	PRO	CON	91-98
HEP[29]	...	...	PRO‡	PRO	...	80-89
Stewart[30]	...	...	PRO‡	PRO‡	...	100-109
NYEC[31]	CON	CON	PRO	PRO	...	$\Delta \geq 17$
EWPHE[32]	...	PRO§	...	PRO§	PRO	...**
PPT[33]	PRO‡§	PRO‡§	PRO‡	PRO‡	...	86-89
IPPPSH[34]	...	...	PRO‡||	PRO‡||	...	92
ANBP[35]	PRO‡§||	PRO‡§||	PRO‡§||	PRO‡§||	...	85-89
MRC[36]	...	...	CON	...	...	Not shown

*PRO indicates findings that support the J-curve hypothesis; and CON, findings that oppose the J-curve hypothesis.
†Abbreviations are expanded in a footnote in Table 1.
‡Incidence and mortality data combined.
§Cardiovascular and cerebrovascular data combined.
||A flattened curve rather than an actual J-shaped curve was seen.
¶Shown for systolic blood pressure only.
#Change in blood pressure from baseline to follow-up.
**Inverse relationship without actual threshold identified.

systolic blood pressure levels also. Most studies have presented cardiovascular outcomes stratified by average achieved treated blood pressure levels. Three studies have presented results by the change in the level of blood pressure achieved from initial readings to follow-up readings.[27,30,31]

Methodological Considerations

To determine whether study results could be used to identify a treatment target level of blood pressure, several issues were considered. One of the most important was whether measurements of treated blood pressure were made prior to ischemic events such as myocardial infarctions. This is because low blood pressure levels often result from these events and, thus, serve as a marker of an underlying prognostic event. In these instances, low blood pressure levels could be the result of ischemic events rather than the cause of future ischemic events. Only three studies limited their analyses to blood pressure measurements that were made prior to cardiovascular events.[30,31,33]

Adjustments for cardiovascular risks and treatment effects associated with cointerventions also were important. Levels of achieved blood pressure may have varying implications depending on whether a subject is a male smoker with an elevated cholesterol level compared with a female who does not smoke and who has a normal cholesterol level. Likewise, a treated blood pressure of 80 mm Hg with associated hypokalemia and uncontrolled diabetes could have a different implication if the hypokalemia and/or hyperglycemia were absent. To assess the true impact of achieved blood pressure control, these factors must be addressed. Although several studies adjusted their results for known baseline cardiovascular risk factors, none considered changes in risk factors or

competing effects of treatment cointerventions made during the course of the study.

Finally, observation times for subjects either must be equal or must not vary with blood pressure control. If follow-up time is shorter or longer in subjects with good or poor control, the outcome of interest could be related to the length of follow-up rather than the achieved blood pressure. Three studies formally addressed inequality in observation times.[27,31,33]

Study Findings

An overview of study findings is given in Table 2. Although some studies have been interpreted previously as not showing a threshold point and/or J-shaped relationship, we did not rely on previous interpretations. Rather, judgments were made by consensus of the four raters after their evaluation of the data stratifications available in the articles. Raters considered a threshold point to be present if the relationship between blood pressure and cardiovascular outcomes was not linear and if the lowest stratification of achieved level of blood pressure was associated with no decrease in cardiovascular events. No consistent J-shaped relationship between treated blood pressure level and stroke incidence or mortality was seen in the studies. However, studies consistently demonstrated a J-shaped relationship between treated diastolic blood pressure and cardiac event incidence and mortality (Fig 1). Only one study[36] failed to show such a relationship, while two[34,35] showed flattened curves at diastolic blood pressures of approximately 85 to 92 mm Hg rather than an actual J-shaped or upswinging curve. Systolic blood pressure relationships often were not addressed or gave conflicting results.

Three studies that received the highest quality ratings and, thus, avoided many of the methodological pitfalls already outlined will be reviewed in detail. The one study that failed to document a J-shaped relationship will be detailed. Finally, a quantitative analysis of the cardiac event data will be presented.

The first study is the Göteborg (Sweden) Primary Prevention Trial,[33] which involved 686 middle-aged men who were followed up for 12 years. Subjects were recruited from a random community sample. They had mild to moderate hypertension and were treated initially with a thiazide, β-blocker, or both. Results were adjusted for baseline risk factors (age, smoking status, cholesterol level, and baseline blood pressure), and only precardiac event blood pressure
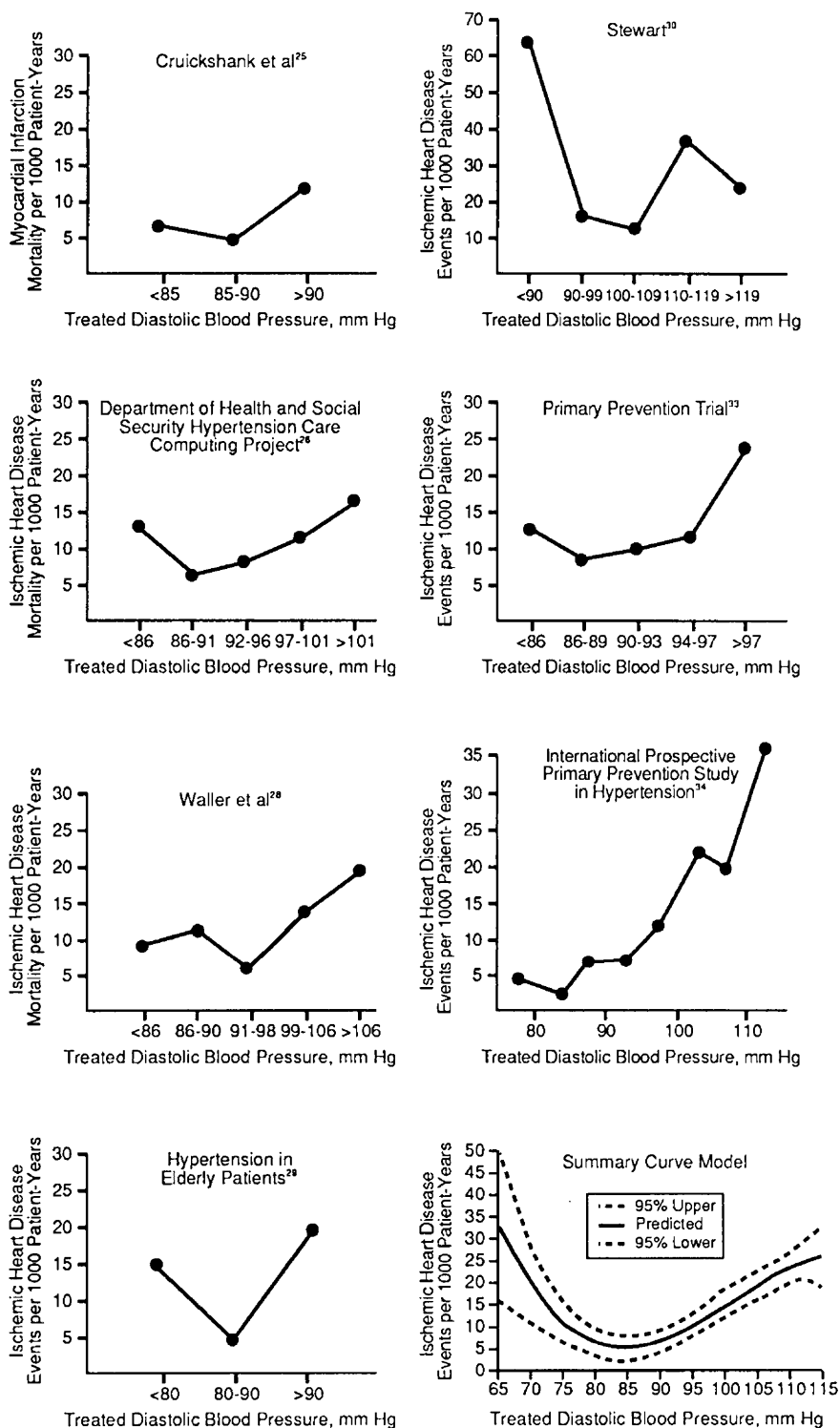

Fig 1.—Studies that stratified cardiac events by treated diastolic blood pressure levels. Ischemic heart disease events is a combination of morbidity and mortality. The summary curve was calculated using a systematic decrease of 10 mm Hg in diastolic blood pressure levels in the study by Stewart[30] because of his use of phase IV diastolic blood pressure measurements; 95% confidence intervals are shown by the surrounding dashed curves.

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measurements were included. Differences in mean follow-up times for people with varying levels of blood pressure control were not statistically significant. Changes in multiple risk factors and associated cointerventions that occurred during the 12-year follow-up were not addressed. A J-shaped relationship that was not statistically significant was found when relating treated diastolic and systolic blood pressure to cerebrovascular and cardiovascular

events defined by combining incidence and mortality data (Fig 1). The relationship was evident in subjects both with and without preexisting coronary heart disease. The nadir of the curve occurred at a treated diastolic blood pressure level of 86 to 89 mm Hg.

The second study is the New York Employee Cohort study,[31] which involved 1765 middle-aged men and women with mild to moderate hypertension. In this study, subjects received a stepped-care approach to treatment using a thiazide, a β-blocker, a calcium channel blocker, or an angiotensin-converting enzyme inhibitor for initial therapy. They were followed up for a mean of 4.2 years. Results were stratified according to change in blood pressure achieved. Varying baseline risks were addressed (age, sex, preexisting cardiovascular disease, race, smoking status, body mass index, cholesterol level, baseline blood pressure, and electrocardiographic results). Only precardiac event blood pressure measurements were related to outcomes, and analyses tried to account for variable lengths of follow-up. A statistically significant J-shaped relationship was found between myocardial infarction incidence and mortality and changes in diastolic blood pressure (Fig 2). A similar trend that was not statistically significant

was observed for systolic blood pressure changes. The J-shaped relationship was observed in people both with and without preexisting cardiovascular disease, but it was more marked in people with known cardiovascular disease. It seemed to be independent of the type of drug therapy used. The nadir or turning point of the curve occurred in subjects who had a moderate drop in blood pressure level with treatment. This moderate drop ranged from 7 to 17 mm Hg.

The third high-quality study is the Hypertension Detection and Follow-up Program,[27] which is a randomized trial that involved more than 10 000 middle-aged men and women with mild to moderate hypertension. Subjects received either stepped care or referred care for their hypertension. After following up patients for 5 years, a statistically significant J-shaped relationship was shown for total mortality related to diastolic blood pressure changes (Fig 3) but not for systolic blood pressure changes. The nadir of the J-shaped curve occurred at a 10- to 19-mm Hg drop in diastolic blood pressure. For people with mild hypertension, minimum risks for mortality occurred with a 10-mm Hg drop. Data to show a J-shaped relationship for cardiac event incidence and/or mortality were not given. Results were
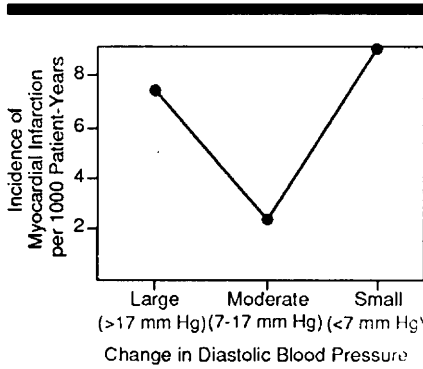

Fig 2.—J-curve relationship between incidence of myocardial infarction and change in diastolic blood pressure (adapted from Alderman et al[31]).

Fig 3.—An increase in mortality is shown in patients with low blood pressure levels (baseline-annuals) enrolled in the Hypertension and Detection Follow-up Program (adapted from Cooper et al[27]).

Fig 4.—A J-curve relationship between mean treated blood pressure and death from myocardial infarction is shown only for patients with preexisting heart disease (adapted from Cruickshank et al[25]).
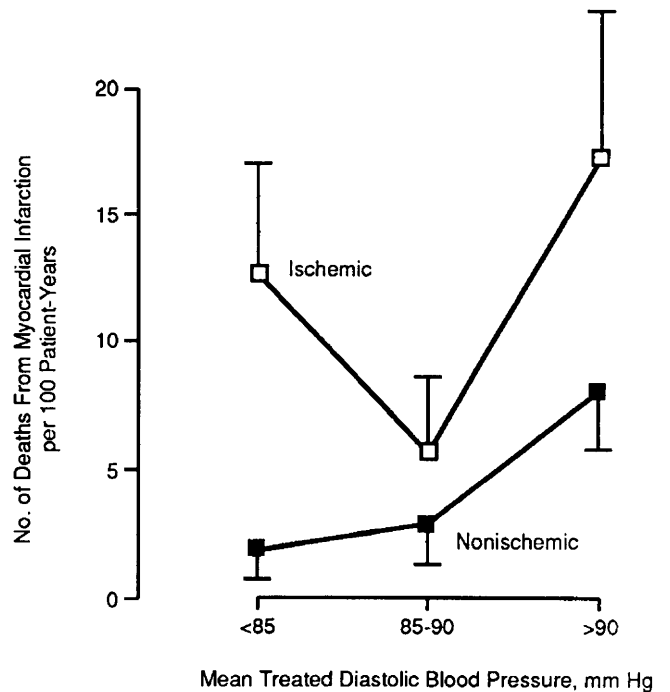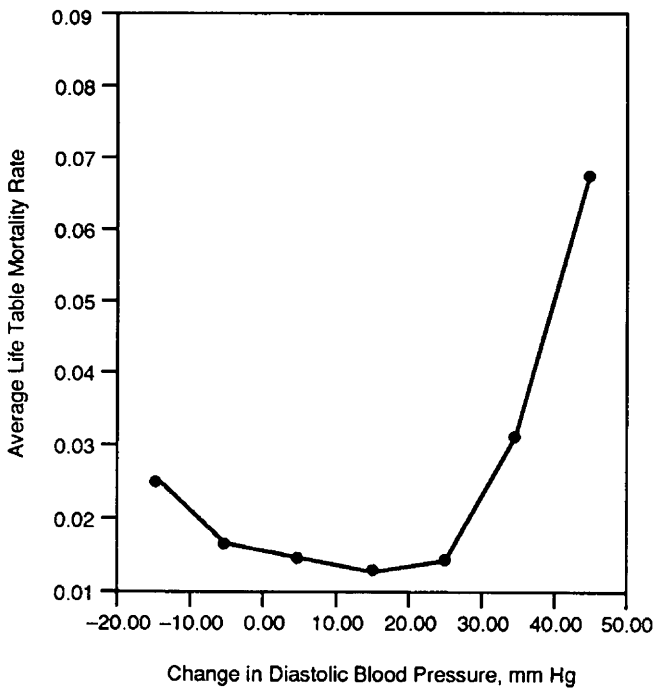
adjusted as necessary for unequal follow-up times and for varying baseline risks and comorbid diseases (age, race, sex, end-organ damage, diabetes, smoking status, ideal body weight, baseline blood pressure, and antihypertensive medication status). Some postevent blood pressure measurements were used.

The only study that failed to confirm a nonlinear relationship between treated diastolic blood pressure and cardiac events was the large Medical Research Council Trial, which involved 17 354 male and female hypertensive subjects.[36] Propranolol and thiazide diuretics were the principle therapeutic agents, and subjects were followed up for 5.5 years. Postevent blood pressure levels and unequal follow-up times were used. Although actual data were not provided in the article, it was reported that there was no significant quadratic effect for diastolic blood pressure in actively treated subjects. The levels of stratification of achieved diastolic blood pressure that were used were unclear, but it seemed that all subjects with pressures less than 90 mm Hg were considered together. Graphs that plotted stroke rates against treated systolic blood pressures suggested a J-shaped relationship in subsets of subjects who were smokers.

Most studies, including those reviewed in detail above, stratified results according to demographic factors (ie, age and sex) and according to risk factors (ie, smoking status). In general, it was impossible to identify whether the J-shaped relationship was specific to certain subgroups such as men, smokers, or middle-aged people. Some studies performed subset analyses limited to subjects with preexisting heart disease. In these analyses, a J-shaped relationship was found for treated blood pressure and cardiac events.[25,26,28,31,33] This finding was most marked in the study by Cruikshank et al,[25] which found a J-shaped curve only in patients with preexisting ischemic disease (Fig 4). However, some of the studies have shown a J-shaped curve, albeit often attenuated, even in subjects without preexisting heart disease.[26,28,30,31,33]

Of particular note, four studies[29,32,35,36] that included placebo or control subjects stratified results by treated and untreated groups. All these studies showed either a J-shaped relationship or a flattened curve in the untreated groups. The European Working Party on High Blood Pressure in the Elderly study[29] showed the J-shaped relationship for total mortality and combined cardiac and cerebrovascular mortality in the placebo group. The Hypertension

in Elderly Patients study[32] and the Medical Research Council Trial[36] had similar results for cardiac mortality and myocardial infarction in a control and placebo group, respectively. In the Medical Research Council Trial, the J-curve relationship was reported only in women in the placebo group; it was not seen in treated subjects.

The graphs of the seven studies[25,26,28-30,33,34] that evaluated cardiac events by levels of treated diastolic blood pressure are seen in Fig 1. (The Medical Research Council Trial is not graphed because actual diastolic blood pressure data were not published.) Four studies[25,26,28,29] evaluated ischemic heart disease mortality independent from morbidity, whereas three[30,33,34] presented only combined event data. The best-fitting summary curves for both the cardiac event (Fig 1) and cardiac mortality data were J shaped. The summary cardiac event curve is given in Fig 1 where person-time event rates equaled -0.001085 diastolic blood pressure^3 $+ 0.3286$ diastolic blood pressure^2 $- 32.26$ diastolic blood pressure $+ 1039.5$. All coefficients were significant ($P<.05$), and the model explained 64% (r^2) of the variability in the data ($P<.05$). The derived nadir of the curve was 84 mm Hg. The predicted cardiac event incidence rates per 1000 person-years were 10.6 and 5.2 at 75 and 85 mm Hg, respectively. This represented a two times higher rate of events for treated blood pressure levels of 75 mm Hg compared with 85 mm Hg. A calculated summary curve for the studies that presented total mortality data by treated blood pressure level was flat, with a plateau of 85 to 90 mm Hg. Of note, this summary curve excluded data from one study[27] that supported a J-curve because such data were presented only by change in treated blood pressure.

COMMENT

In summary, 13 studies that involved more than 48 000 subjects with treated hypertension have stratified their outcomes by achieved blood pressure levels. These studies have shown that there is not a consistent J-shaped relationship between treated blood pressure level and stroke, but that a consistent J-shaped relationship is apparent for cardiac events and treated diastolic blood pressure level. It is possible that this relationship is most marked in subjects with preexisting cardiac disease. In addition, the J-shaped relationship has been observed consistently in control subjects in these studies. This suggests that the J-curve phenomena, whether occurring biologically or thera-

peutically, may explain increased cardiac mortality. More important, it suggests that the J-curve is "probably independent of treatment and that it reflects a relation between cardiac events and absolute diastolic blood pressure with treatment merely shifting ischemic hypertensive subjects from a fairly safe part to a less safe part of the curve."[40]

The exact mechanism by which lowering blood pressure levels beyond a critical point could increase cardiovascular complications is unknown. However, several pathophysiological mechanisms have been proposed.[2] First, as many as 50% of hypertensive patients have left ventricular hypertrophy. A hypertrophied ventricle has increased myocardial oxygen consumption compared with a normal ventricle. If a decrease in coronary flow occurs as a result of lowered diastolic blood pressure, a hypertrophied ventricle may become ischemic before a normal ventricle and may be prone to ischemic events. Second, in the coronary circulation, oxygen extraction at baseline may be at near maximum capacity. In low flow situations the heart may not compensate by increasing oxygen extraction. Third, autoregulation, the primary defense mechanism in patients with coronary artery disease, is adversely affected by low diastolic blood pressures. Normally, when a large coronary artery becomes stenotic, the smaller distal arteries dilate or autoregulate. This distal dilation decreases resistance and improves flow. If coronary perfusion pressure is lowered by overaggressive hypertensive therapy, the vessels may not further autoregulate and ischemia may develop. Fourth, excessive lowering of the diastolic blood pressure leading to low coronary flow may cause increased blood viscosity and increased platelet adhesiveness that could lead to thrombus formation, a keystone event in the development of myocardial infarction. Last, areas of well-perfused myocardium adjacent to areas of ischemic myocardium precipitated by low diastolic blood pressures may cause a buildup of metabolic gradients, giving rise to ventricular dysrrhythmias.

Whether the data examined in this review can be used to infer an optimal treatment goal in hypertensive subjects is debatable. The studies were not originally designed to specifically establish a treatment goal. No clinical trial has been performed that has randomized hypertensive subjects to study arms with different treatment targets, although one such trial is in progress.[41] Thus, the data considered in this review are subject to various limitations often

inherent in any secondary data analysis. Although several of the studies attempted to control for potential limitations, most did not control for metabolic side effects of therapy such as hypokalemia, hyperlipidemia, and hyperglycemia, and none controlled for changes in risk factors or for associated cointerventions that could have affected cardiovascular outcomes. These factors could account for the observed J-shaped relationships and, thus, could serve as confounders in using the study findings to determine treatment goals.

In summary, it is clear from randomized trials that treating hypertension reduces cardiovascular events. Whether there is a threshold point beyond which subjects should not be treated is not established. However, clinicians must make decisions even in the face of imperfect data. Lacking a randomized trial that evaluates different treatment thresholds, we can and should take advantage of existing information to guide us in our therapeutic decision making. As existing data do not suggest a consistent J-shaped relationship between stroke and treated blood pressure, it is reasonable to consider reducing blood pressure to conventional levels (70 to 90 mm Hg) to prevent strokes and their attendant mortality. Unfortunately, such reductions may be deleterious in precipitating cardiac events, particularly in patients with known cardiac disease. One may then be faced with the uncomfortable choice of whether to attempt to prevent cerebrovascular events at the expense of cardiac events or vice versa. As increased cardiac morbidity and mortality related to blood pressure treatment, if it occurs, may be most marked in subjects with preexisting cardiac disease, a reasonable current compromise is to be cautious in lowering blood pressure levels below 85 mm Hg in patients with known ischemic heart disease. The prudence of this tactic is accentuated by the conspicuous lack of evidence of benefit for therapeutically lowering blood pressure levels beyond this threshold.

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