Annals of Internal Medicine | ARTICLE

Dogma Disputed: Can Aggressively Lowering Blood Pressure in Hypertensive Patients with Coronary Artery Disease Be Dangerous?

Franz H. Messerli, MD; Giuseppe Mancia, MD; C. Richard Conti, MD; Ann C. Hewkin, MSc; Stuart Kupfer, MD; Annette Champion, MBA; Rainer Kolloch, MD; Athanase Benetos, MD; and Carl J. Pepine, MD

Background: Because coronary perfusion occurs mainly during diastole, patients with coronary artery disease (CAD) could be at increased risk for coronary events if diastolic pressure falls below critical levels.

Objective: To determine whether low blood pressure could be associated with excess mortality and morbidity in this population.

Design: A secondary analysis of data from the International Verapamil-Trandolapril Study (INVEST), which was conducted from September 1997 to February 2003.

Setting: 862 sites in 14 countries.

Patients: 22 576 patients with hypertension and CAD.

Interventions: Patients from INVEST were randomly assigned to a verapamil sustained-release– or atenolol-based strategy; blood pressure control and outcomes were equivalent.

Measurements: An unadjusted quadratic proportional hazards model was used to evaluate the relationship between average on-treatment blood pressure and risk for the primary outcome (all-cause death, nonfatal stroke, and nonfatal myocardial infarction [MI]), all-cause death, total MI, and total stroke. A second model adjusted for differences in baseline covariates.

Results: The relationship between blood pressure and the primary outcome, all-cause death, and total MI was J-shaped, particularly for diastolic pressure, with a nadir at 119/84 mm Hg. After adjustment, the J-shaped relationship persisted between diastolic pressure and primary outcome. The MI–stroke ratio remained constant over a wide blood pressure range, but at a lower diastolic blood pressure, there were substantially more MIs than strokes. An interaction between decreased diastolic pressure and history of revascularization was observed; low diastolic pressure was associated with a relatively lower risk for the primary outcome in patients with revascularization than in those without revascularization.

Limitations: This is a post hoc analysis of hypertensive patients with CAD.

Conclusions: The risk for the primary outcome, all-cause death, and MI, but not stroke, progressively increased with low diastolic blood pressure. Excessive reduction in diastolic pressure should be avoided in patients with CAD who are being treated for hypertension.

Ann Intern Med. 2006;144:884-893. www.annals.org
For author affiliations, see end of text.
ClinicalTrial.gov identifier: NCT00133692.

For 2 decades, the hypertension literature has been haunted by the phenomenon of a "paradoxical" increase in morbidity and mortality with an excessive decrease in blood pressure (J-curve). Indeed, several reports have shown that low diastolic pressure is associated with an increased risk for coronary heart disease and related mortality in older adults and in patients taking antihypertensive medications (1–13). After doing a review and meta-analysis of pertinent studies, Farnett and colleagues (14) concluded that although there was no consistent J-shaped relationship between stroke and systolic or diastolic pressure, there was a consistent J-shaped relationship for cardiac events and diastolic pressure. These authors stated that this dichotomy in the relationship between diastolic pressure and target organ disease may "leave a clinician with the uncomfortable choice of whether to prevent stroke or renal disease at the expense of coronary heart disease." These findings were at variance with the generally accepted dogma formulated by the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) (15), which stated that the relationship between pressure and risk was "strong, continuous, independent, predictive and etiologically significant." Within the past decade, the phenomenon of a J-curve has been studied in several large trials of normotensive and hypertensive patients (16–30).

Not surprisingly, arguments regarding whether a J-curve could be clinically significant have become somewhat contentious. That is, some rely on evidence that on-treatment diastolic pressure below 70 mm Hg does not increase risk for cardiovascular disease and thus deny an impairment of vital organ perfusion within the usual values achievable by antihypertensive treatment. Others, however, consider the J-curve a more real possibility, particularly for the heart. In contrast to other organs, the heart is perfused mostly during diastole and thus could be more vulnerable to diastolic pressure reduction. If a J-curve did exist, it should be most evident in patients with limited coronary perfusion, in other words, in those with manifest coronary artery disease (CAD). Optimal blood pressure in patients with hypertension and CAD remains controversial because few randomized clinical trials have been done in this population (31, 32). The International Verapamil-Trandola-

See also:

Print
Editors' Notes 885

Web-Only
Conversion of figures and table into slides

pril Study (INVEST) (33), a randomized trial, evaluated more than 22 000 patients with CAD and hypertension. This patient profile, together with unprecedented levels of blood pressure control, provided a unique opportunity to critically investigate the hypothesis that the risk for CAD would increase with an excessive decrease in diastolic pressure.

METHODS

Study Design and Intervention

The INVEST design, methods, and principal results have been previously published (33). The trial used an open design with blinded end point assessment. In brief, clinically stable patients with CAD and hypertension were randomly assigned to a verapamil sustained-release–based or atenolol-based strategy. Patients with previous myocardial infarction (MI) within 3 months of enrollment or class IV or V congestive heart failure were excluded. Blood pressure goals were based on JNC VI (systolic pressure <140 mm Hg and diastolic pressure <90 mm Hg or systolic pressure <130 mm Hg and diastolic pressure <85 mm Hg in patients with diabetes or renal impairment) (15). The addition of trandolapril or hydrochlorothiazide was recommended when necessary to achieve blood pressure goals. Trandolapril was also recommended for patients with heart failure, diabetes, or renal impairment.

Documented CAD was defined as any of the following: remote (≥3 months before enrollment) confirmed MI, coronary angiography showing more than 50% narrowing of at least 1 major coronary artery, diagnosis of classic angina pectoris, or concordant abnormalities on 2 different signals (electrocardiography, echocardiography, or radionuclide scans) from stress test findings concordant for ischemia (for example, ST-segment depression or perfusion defects on radionuclide scanning or wall-motion abnormalities on echocardiography or radionuclide scanning).

Patient Monitoring and Follow-up

Protocol visits were scheduled every 6 weeks for the first 6 months and then biannually until 2 years after the last patient was enrolled. Patients were assessed for response to treatment, symptoms, treatment adherence, and adverse effects at each visit and at the end of the study as detailed elsewhere (33). Patient follow-up was complete when we received a final assessment form through the online data system or a death report. The Internet-based electronic data collection method used in INVEST did not accept the entry until all required fields were complete.

Blood pressure was measured by using a standard mercury sphygmomanometer with an appropriately sized cuff applied to the upper nondominant arm at heart level. By auscultation at the brachial artery, systolic pressure was recorded at the first Korotkoff sound and diastolic pressure was recorded at the disappearance of the fifth Korotkoff sound. Blood pressure was measured twice, at least 2 minutes apart, and the measurements were averaged.

Context

Experts debate the consequences of "excessive" lowering of diastolic pressure in patients with hypertension and coronary artery disease.

Contribution

This report is a secondary analysis of data from a large trial of 2 antihypertensive drug regimens in patients with known coronary artery disease. The authors found a J-shaped relationship between diastolic blood pressure and all-cause death and myocardial infarction, with the increased risk occurring at diastolic blood pressures below 70 to 80 mm Hg, that is, the lower the diastolic pressure, the higher the risk.

Cautions

The study examined associations between blood pressure and outcomes; it could not prove that the antihypertensive therapy that lowered diastolic pressure "too much" caused the adverse outcomes.

—The Editors

Study Outcomes

The primary outcome was the first occurrence of all-cause death, nonfatal MI, or nonfatal stroke by intention-to-treat analysis. The MI and stroke definitions are detailed elsewhere (34). These 3 components individually were the main secondary outcomes. For this analysis, additional outcomes included fatal and nonfatal MI, fatal and nonfatal stroke, and average on-treatment blood pressure before outcome or censoring. Ascertainment and blinded adjudication of outcomes were described previously (32). Follow-up data were available for 22 008 (97.5%) patients.

Statistical Analysis

The main conclusions of INVEST were that the 2 treatment strategies were equivalent with respect to the primary outcome, main secondary outcomes, and on-treatment systolic and diastolic pressures. Thus, data for all enrolled patients were combined and included in these analyses following the intention-to-treat principle. A P value of 0.05 or less was considered statistically significant. Patients without a primary outcome event were censored at their latest follow-up visit. Average follow-up systolic and diastolic pressures were calculated for each patient by using all post-baseline results, up to the date of primary outcome or censoring. The baseline value was substituted for patients with no post-baseline data ($n = 1154$).

In this exploratory analysis, the proportions of patients were pooled by 10–mm Hg strata of average follow-up systolic pressure, and the distribution of primary outcome event rate was evaluated to determine whether the relationship was linear. A similar presentation was prepared for diastolic pressure. Because the frequency distributions seemed consistent with a quadratic curve, a quadratic Cox

Table. **Demographic and Baseline Characteristics by Systolic Blood Pressure and Diastolic Blood Pressure Categories**

Variable	Mean Systolic Blood Pressure Category						
	≤110 mm Hg (*n* = 234)	>110–≤120 mm Hg (*n* = 1709)	>120–≤130 mm Hg (*n* = 6859)	>130–≤140 mm Hg (*n* = 7216)	>140–≤150 mm Hg (*n* = 3737)	≥150–≤160 mm Hg (*n* = 1663)	>160 mm Hg (*n* = 1157)
Mean age (SD), *y*	65.6 (10.5)	64.4 (9.7)	65.0 (9.6)	66.2 (9.6)	67.4 (9.6)	67.6 (10.0)	67.7 (10.2)
Mean body mass index (SD), kg/m^2	27.6 (5.7)	28.3 (10.7)	28.7 (5.3)	29.4 (8.2)	29.7 (6.4)	29.7 (6.0)	29.6 (6.3)
Women, %	43.6	46.5	50.4	52.1	54.3	57.7	57.6
White, %	51.3	42.9	42.3	51.0	54.4	52.4	50.8
Myocardial infarction, %	47.9	37.9	31.1	30.1	32.8	32.5	33.5
Coronary artery bypass graft or angioplasty, %	32.9	26.1	24.3	27.9	31.0	29.2	28.0
Stroke or transient ischemic attack, %	8.5	7.2	6.2	7.1	7.5	8.5	10.6
Left ventricular hypertrophy, %*	28.6	27.2	22.1	19.8	20.6	24.4	25.6
Class I–III heart failure, %	15.0	9.1	5.3	4.4	5.1	6.7	7.1
Diabetes, %†	22.2	26.7	26.9	27.1	29.9	34.5	34.3
Cancer, %	6.8	3.1	2.8	3.2	4.1	4.0	3.7

* Based on patient history.
† History of diabetes or use of insulin or oral hypoglycemic medication.

proportional hazards model was formed for the time to primary outcome for each blood pressure variable, with factors for blood pressure and blood pressure squared. Similarly, the relationship between each 10–mm Hg stratum of average systolic pressure and diastolic pressure and all-cause death, fatal and nonfatal MI, and fatal and nonfatal stroke was evaluated. For the time to primary outcome, a second model was fitted, adjusting for the following baseline covariates: age (10-year increments), sex, race and ethnicity (white, Asian, black, Hispanic, multiracial, or other), previous MI, heart failure (classes I to III), body mass index in increments of 5 kg/m^2, U.S. residency, renal impairment, peripheral vascular disease, left ventricular hypertrophy, smoking history, coronary revascularization, dyslipidemia, stroke or transient ischemic attack, angina pectoris, arrhythmia, diabetes, cancer, aspirin use, and average systolic pressure or diastolic pressure and systolic pressure squared or diastolic pressure squared.

To identify clinically relevant interactions between the J-shaped curve and baseline diastolic pressure, demographic characteristics, and comorbid conditions for the primary outcome, a 2-step procedure was used. First, baseline covariates were tested individually by adding the variable and 2 interaction terms (variable × diastolic pressure and variable × [diastolic pressure squared]) to the Cox proportional hazards model. Variables included were age older than 70 years, sex, previous MI, heart failure (classes I to III), previous stroke or transient ischemic attack, diabetes, cancer, renal impairment, hypercholesterolemia, peripheral vascular disease, smoking history, U.S. residency, body mass index greater than 29 kg/m^2 (mean baseline body mass index), and diastolic pressure greater than 86 mm Hg (mean baseline diastolic pressure). The change in log likelihood was used to assess the significance of simultaneously adding the 2 interaction terms. The second step in identifying clinically relevant interactions between the J-shaped curve and baseline covariates was to plot the hazard ratios for the primary outcome versus diastolic pressure in the presence or absence of the statistically significant interacting baseline factor. For these plots, the original model with factors for diastolic pressure and diastolic pressure squared was formed for 2 separate subgroups, for patients with and those without the variable of interest. Because the target diastolic pressure for most patients during the study was less than 90 mm Hg, estimated hazard ratios were calculated with reference to 90 mm Hg to standardize the results from the 2 models.

Role of the Funding Source

Investigators at the University of Florida conceived and designed INVEST before seeking sponsorship. BASF Pharma/Knoll AG, later Abbott, sponsored the trial but played no part in study conduct or data collection; the database was maintained and completed at the University of Florida. Dr. Messerli and coauthors had full access to the data, and this manuscript represents their interpretation of a secondary analysis.

RESULTS

The **Table** shows demographic data and baseline characteristics of patients by systolic pressure and diastolic pressure categories. Patients with low systolic pressure tended to be leaner and male and had a higher incidence of MI, cancer, and heart failure than did those with high systolic pressure. Patients with low diastolic pressure tended to be older, leaner, female, and white and had a higher incidence of MI, cancer, heart failure, and diabetes compared with those with high diastolic pressure.

After follow-up of 61 835 patient-years (median, 2.7 years/patient), 2269 patients had a primary outcome event

Table—Continued

Mean Diastolic Blood Pressure Category						
≤60 mm Hg (*n* = 176)	>60–≤70 mm Hg (*n* = 2239)	>70–≤80 mm Hg (*n* = 11 306)	>80–≤90 mm Hg (*n* = 7376)	>90–≤100 mm Hg (*n* = 1230)	≥100–≤110 mm Hg (*n* = 202)	>110 mm Hg (*n* = 46)
73.7 (8.9)	71.1 (9.3)	67.0 (9.6)	63.8 (9.2)	61.6 (9.1)	60.8 (9.0)	57.9 (7.1)
28.6 (6.4)	28.0 (5.3)	28.8 (8.2)	29.9 (5.8)	30.6 (6.3)	30.9 (6.3)	30.9 (6.4)
56.8	48.5	53.1	52.2	49.0	53.5	41.3
71.6	67.8	48.2	44.0	40.7	34.2	28.3
47.2	41.0	32.0	29.0	30.9	33.7	26.1
47.7	43.6	27.6	23.1	19.7	15.8	4.3
11.9	9.6	7.3	6.3	6.5	9.4	8.7
22.7	21.3	21.4	22.0	25.0	29.7	37.0
21.6	9.5	5.3	4.3	5.9	7.9	2.2
44.3	36.6	28.5	25.9	25.2	26.2	17.4
10.8	6.9	3.4	2.4	1.9	1.5	2.2

(10.1%) (33). During the study, patients receiving the verapamil sustained-release–based and atenolol-based strategies had similar blood pressure and cardiovascular outcomes (33). The frequency of the primary outcome was related to systolic pressure and diastolic pressure in a J-shaped pattern (**Figure 1**). Similar J-curves were observed for both treatment strategies (data not shown). The pattern of the J-curve differed between systolic pressure and diastolic pressure and the primary outcome in that the J-curve was relatively shallow for systolic pressure. Lower diastolic pressure led to almost doubled and tripled risk for the primary outcome in the diastolic pressure strata of greater than 60 mm Hg to 70 mm Hg or less (17.4%) and 60 mm Hg or less (31.8%), respectively (**Figure 1**). Those with diastolic pressure of 70 mm Hg or less made up only 10.7% (2415 of 22 576) of patients but accounted for 19.6% (445 of 2268) of primary outcome events (**Figure 1**). The increased risk for the primary outcome in patients with a diastolic pressure of 70 mm Hg or less could not be attributed solely to increasing systolic pressure levels because the mean systolic pressure in patients who experienced this outcome decreased with a decrease in diastolic blood pressure, although not proportionally (**Figure 1**).

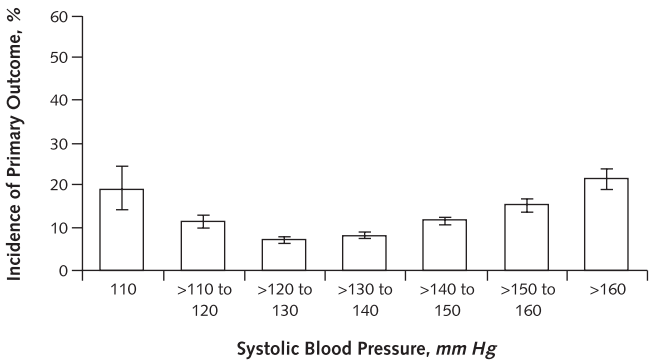
The hazard ratios from the unadjusted Cox proportional hazards model for the primary outcome showed a blood pressure nadir at 119/84 mm Hg. The optimal range of hazard ratios for systolic pressure and the primary outcome was much shallower for systolic pressure than for diastolic pressure and thus extended to a relatively low systolic pressure (**Figure 2**, *top*).

In the adjusted models for time to primary outcome, the J-curve remains with a blood pressure nadir estimated at 129/74 mm Hg (**Figure 2**, *middle*); however, there is a more shallow relationship between the decrease in diastolic blood pressure and primary outcome than in the unadjusted models. For both adjusted models, the baseline covariate with the highest individual hazard ratio estimate was heart failure (1.92 in the systolic pressure model and 1.94 in the diastolic pressure model), indicating an almost doubled risk for the primary outcome after adjusting for blood pressure. However, the interactions of baseline heart failure with systolic pressure and systolic pressure squared were not statistically significant when added to this model. A similar observation was made for the diastolic pressure model. The bottom panel of **Figure 2** shows the relative risk for reduced or increased blood pressure adjusted for differences in baseline heart failure, with a nadir estimated at 116/83 mm Hg. For diastolic pressure, adjusting for baseline heart failure alone slightly reduced the relative level of risk but did not change the shape of the curve compared with the unadjusted analysis.

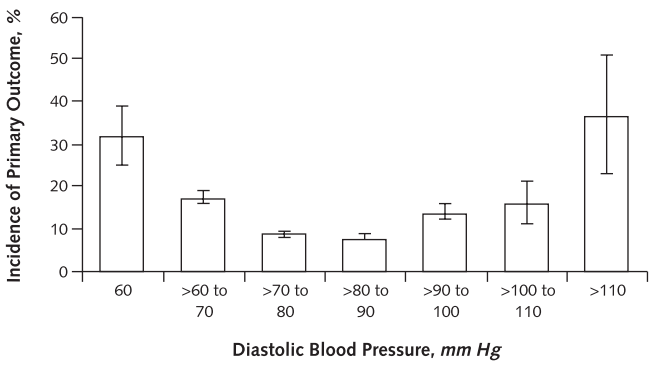
A J-shaped relationship with diastolic pressure was also observed for death from all causes (the outcome that accounted for the highest proportion of events in the primary outcome; data not shown); for MI (fatal and nonfatal); and to a much lesser extent for stroke (fatal and nonfatal) (**Figure 3**). The incidence ratio between MI and stroke remained remarkably constant over a wide range of blood pressure strata. However, this ratio increased with a progressive decrease in diastolic blood pressure (**Figure 3**). The preponderance of MI over stroke with progressively decreasing diastolic blood pressure suggests that the compromised coronary perfusion resulting from low diastolic blood pressure could be a factor.

Interactions between diastolic pressure and the primary outcome were statistically significant only for U.S. residency, hypercholesterolemia, previous revascularization, and diabetes. Sex ($P = 0.050$) and smoking history ($P = 0.080$) were borderline significant ($P < 0.1$). Analysis of hazard ratios for the primary outcome versus diastolic

Figure 1. **Incidence of the primary outcome (first occurrence of all-cause death, nonfatal myocardial infarction, or nonfatal stroke) by systolic blood pressure and diastolic blood pressure strata.**



Patients with primary outcome, *n*	45	196	493	596	437	253	248
Total patients, *n*	234	1709	6859	7216	3737	1663	1157
Mean diastolic blood pressure, *mm Hg*							
Patients with primary outcome	65.7	70.8	74.4	76.8	79.6	81.7	89.1
Patients without primary outcome	67.9	73.5	76.7	78.9	81.3	84.6	90.4



Patients with primary outcome, *n*	56	389	1003	596	174	33	17
Total patients, *n*	176	2239	11 306	7376	1230	202	46
Mean systolic blood pressure, *mm Hg*							
Patients with primary outcome	124.3	131.7	135.1	143.7	160.2	171.6	186.0
Patients without primary outcome	127.0	129.1	131.0	138.8	154.2	169.4	187.5

Error bars represent 95% CIs.

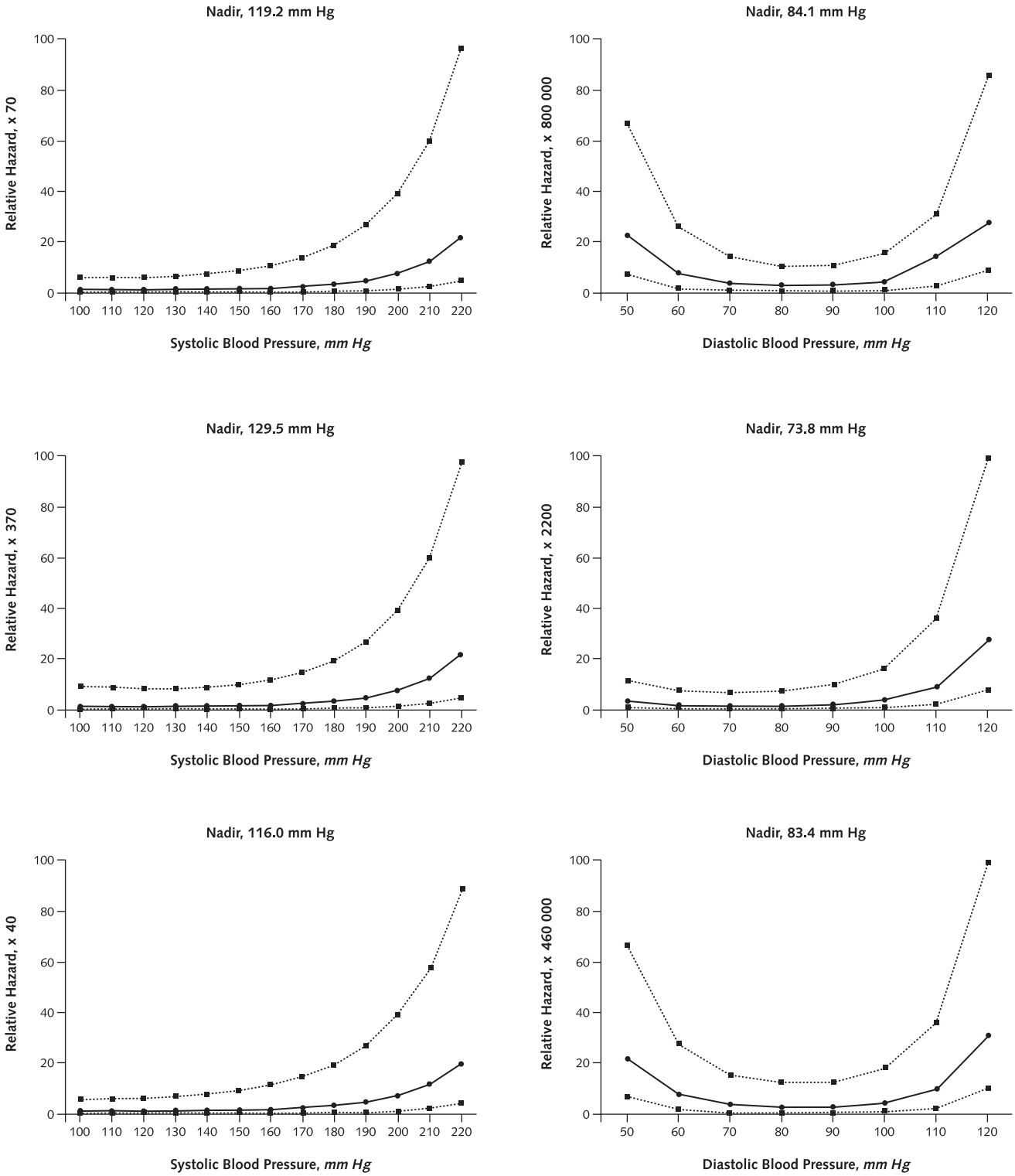
blood pressure plots indicated that with the exception of coronary revascularization, all statistically significant interactions occurred with increasing levels of diastolic pressure only (**Figure** 4). Thus, the absence of U.S. residency and the presence of hypercholesterolemia or diabetes were associated with a relatively higher risk for the primary outcome with increasing diastolic pressure. In contrast, revascularization interacted with the relationship between diastolic pressure and risk for the primary outcome only as diastolic pressure decreased, suggesting that patients who had revascularization before enrollment tolerated lower diastolic pressure relatively better than those who did not have revascularization.

The treatment strategy showed no interaction with diastolic pressure. The J-curves of patients in the verapamil group were not different from those of patients in the atenolol group.

DISCUSSION

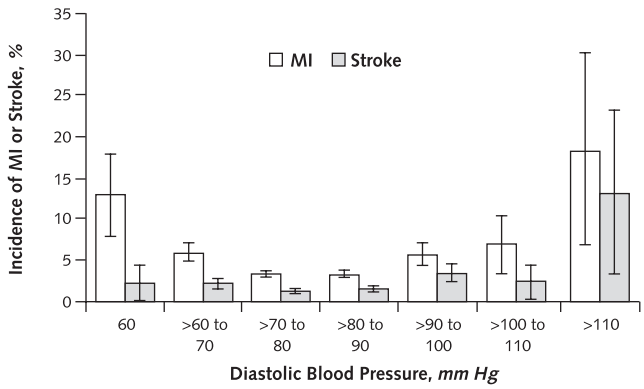
Three pathophysiologic mechanisms have been proposed to explain the existence of a J-curve: 1) Low diastolic pressure could compromise blood flow to target organs, impairing coronary perfusion and causing cardiac ischemia; 2) low diastolic pressure could result from an increase in pulse pressure, reflecting stiffness of large arteries and representing a marker for advanced vascular disease; and 3) low diastolic pressure could be an epiphenomenon related

Figure 2. **Unadjusted and adjusted hazard ratios for the primary outcome by systolic blood pressure and diastolic blood pressure strata.**



The CIs are plotted as dotted lines. See text for further details.

Figure 3. **Incidence of total myocardial infarction (*MI*) and total stroke by diastolic blood pressure strata.**



MI							
Patients with MI, *n*	23	135	387	255	71	14	8
Total patients, *n*	177	2239	11 324	7378	1214	201	43
Mean systolic blood pressure, *mm Hg*							
Patients with MI	127.0	131.9	135.2	143.8	158.3	166.9	191.4
Patients without MI	126.2	129.6	131.4	139.3	155.2	170.3	185.7
Stroke							
Patients with stroke, *n*	4	50	151	116	44	5	6
Total patients, *n*	175	2253	11 320	7366	1217	199	45
Mean systolic blood pressure, *mm Hg*							
Patients with stroke	112.2	132.7	136.3	143.8	161.1	171.1	177.9
Patients without stroke	126.7	129.6	131.5	139.3	155.2	169.9	187.9

Error bars represent 95% CIs.

to underlying chronic illness, thereby increasing morbidity and mortality (reverse causality). The 22 576–patient INVEST (33) provides a unique opportunity to analyze the relationship between blood pressure and outcome and the underlying mechanisms of the J-curve. All patients in INVEST had established CAD and hypertension; blood pressure control was unprecedented in INVEST (compared with the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial [ALLHAT] [35]; for instance, in INVEST, 18% more patients achieved systolic pressure goals as defined by JNC VI); both therapeutic strategies in INVEST are coronary-protective (36–41); and the INVEST therapeutic strategies had equivalent adverse outcomes while providing the same blood pressure control.

We observed a J-shaped relationship between systolic pressure and diastolic pressure and the primary outcome (all-cause death, nonfatal MI, or nonfatal stroke). Clearly, the diastolic J-curve was much more pronounced than the systolic J-curve. A similar J-shaped relationship was observed between diastolic pressure and all-cause death, the outcome that accounted for the highest proportion of events in patients with the primary outcome. Conceivably, the 2 J-type relationships between primary outcome and systolic pressure and diastolic pressure, respectively, could be explained to some extent by any of the 3 pathophysiologic mechanisms mentioned earlier, singly or in combination. Thus, our observation of a J-curve in patients with CAD receiving treatment for hypertension does not establish a causal relationship, nor does it allow the conclusion that an inappropriate decrease in diastolic pressure with antihypertensive therapy causes the excessive morbidity and mortality. However, these findings emphasize that hypertensive patients with CAD and a lower diastolic pressure are at increased risk. Because perfusion occurs mostly during diastole, physiologic features of myocardial perfusion are unique and therefore are directly related to diastolic pressure. Consequently, an inappropriately low diastolic pressure beyond a certain critical level could compromise myocardial perfusion. Owens and O'Brien (42), monitoring patients with electrocardiography and ambulatory blood pressure devices over a period of 24 hours, showed that in 13 of 14 instances, ischemic events were related to diastolic rather than systolic hypotension. They concluded that symptomatic and silent ischemia occurred in a temporally causal relationship with diastolic hypotension.

As in the Framingham cohort (43), pulse pressure was a powerful determinant of the risk for primary outcome in INVEST (44). Furthermore, when pulse pressure was added to the diastolic pressure model in an exploratory analysis, pulse pressure and diastolic blood pressure were statistically significantly associated with the primary outcome (44). In contrast to the Framingham cohort, systolic pressure decreased in parallel with the decrease in diastolic pressure in INVEST, although this decrease was not pro-

portional. This, together with an increased preponderance of MI over stroke in patients with a diastolic pressure below 70 mm Hg, argues against pulse pressure being the sole cause of increased CAD in those with low diastolic pressure. The blood pressure nadir associated with the lowest risk for the primary outcome was 119/84 mm Hg, which is remarkably close to the nadir of 138.5/82.6 mm Hg for diastolic pressure observed in the Hypertension Optimal Treatment (HOT) trial (45).

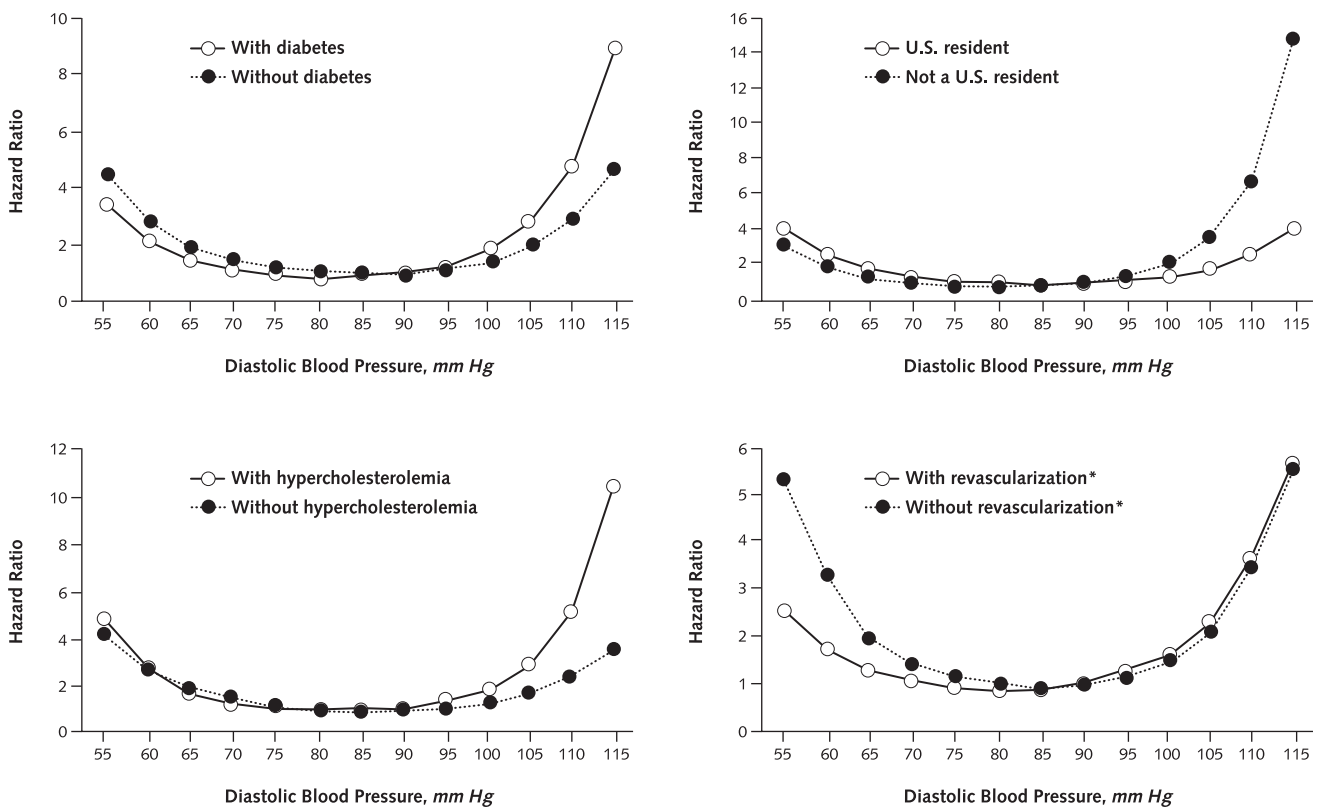
These findings indicate that in this sample of patients with CAD, diastolic pressure below 70 to 80 mm Hg could potentially be harmful. Similarly, the National Health and Nutrition Examination Survey (NHANES) showed a J-curve between diastolic pressure and cardiovascular mortality in patients older than 55 years, even after correcting for regression dilution bias and removing confounders, such as patients with serious illnesses (46). A very robust J-shaped relationship was also documented in the Irbesartan Diabetic Nephropathy Trial (IDNT); for every decrease of 10 mm Hg in diastolic pressure, the relative risk for MI increased by 61% (47).

Absence of U.S. residency and presence of hypercholesterolemia or diabetes were associated with a higher risk for the primary outcome in groups with diastolic pressure above 90 mm Hg. In contrast, revascularization interacted with diastolic pressure and the risk for the primary outcome only with a lower blood pressure. Hence, patients who were not U.S. residents or those with a history of hypercholesterolemia or diabetes are at relatively higher risk for the primary outcome with increasing diastolic pressure, whereas patients who had coronary revascularization seem to tolerate lower diastolic pressure relatively better than those without coronary revascularization. The interaction of coronary revascularization with diastolic pressure supports the hypothesis that myocardial perfusion may be compromised at low diastolic pressures, but less so in patients who have previously had revascularization.

It may seem reassuring that our analysis of the data from INVEST suggests that the critical range of systolic and diastolic pressures was relatively low. However, both drug strategies in INVEST have been shown to protect the heart, perhaps because they reduce heart rate; prolong diastole; and, at least for verapamil, may have a direct arteriolar dilatory and anticoronary spasm effect that maintains coronary blood flow (36–40). Antihypertensive medications without these features, particularly drugs that increase heart rate, have the potential to compromise myocardial perfusion at higher diastolic pressures than did verapamil and atenolol in INVEST.

Our findings are limited to hypertensive patients with

Figure 4. **Analysis of clinically significant interactions of baseline covariates and diastolic blood pressure for the primary outcome.**



*Coronary artery bypass graft or percutaneous coronary intervention.

CAD who were treated with either verapamil sustained-release–based or atenolol-based strategies. The assessment of the effects of blood pressure on outcomes in these patients with CAD was a secondary analysis in INVEST. This exploratory analysis assumes a quadratic relationship between blood pressure values and outcome.

Our analysis showed that in hypertensive patients with CAD who were treated with sustained-release verapamil or atenolol to lower blood pressure, increased risk for all-cause death and MI was associated with diastolic pressure below 70 to 80 mm Hg. Although elevated systolic pressure, one of the most powerful risk factors for stroke and MI, remains undertreated in many patients, our data suggest caution with excessive lowering of diastolic pressure in hypertensive patients with CAD. These findings lend credence to the cautious statement of JNC 7 (48) (as opposed to the statement of JNC VI [15]) that "patients with occlusive CAD are put at risk of coronary events if diastolic blood pressure is low."

From St. Luke's-Roosevelt Hospital, New York, New York; University of Milan, Milan, Italy; University of Florida, Gainesville, Florida; Abbott, Abbott Park, Illinois; Medizinische Klinik, Bielefeld, Germany; and Hôpital Brabois, University of Nancy, Nancy, France.

Note: The first author, Dr. Messerli, has had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Grant Support: By research grants from Abbott.

Potential Financial Conflicts of Interest: *Employment:* F.H. Messerli (Abbott, Novartis, Pfizer Inc., Sankyo), A.C. Hewkin (Abbott), S. Kupfer (Abbott), A. Champion (Abbott); *Consultancies:* F.H. Messerli (Abbott, Norvartis, Pfizer Inc., Merck & Co. Inc.), C.J. Pepine (Abbott Laboratories, CV Therapeutics); *Honoraria:* G. Mancia (Pfizer Inc., Novartis Pharma, Sanofi-Synthelabo, Servier, Abbott, Merck Sharp & Dohme, Bayer, Boehringer Ingelheim), A. Benetos (Abbott, Servier, Bayer); *Stock ownership or options (other than mutual funds):* A.C. Hewkin (Abbott), S. Kupfer (Abbott), A. Champion (Abbott); *Expert testimony:* F.H. Messerli (Novartis); *Grants received:* F.H. Messerli (Novartis), C.J. Pepine (Abbott Laboratories, AstraZeneca, Berlex Laboratories Inc., CV Therapeutics, GlaxoSmithKline, King Pharmaceuticals Inc., Millennium Pharmaceuticals, Inc., Monarch Pharmaceuticals, Pfizer, Sanofi-Aventis, Schering-Plough, Wyeth-Ayerst Laboratories); *Grants pending:* F.H. Messerli (GlaxoSmithKline); *Patents received:* C.J. Pepine (University of Florida). Abbott markets 2 of the study drugs (verapamil and trandolapril) and their fixed-dose combination.

Requests for Single Reprints: Franz H. Messerli, MD, Division of Cardiology, St. Luke's-Roosevelt Hospital, 1000 Tenth Avenue, New York, NY 10019; e-mail, Fmesserli@aol.com.

Current author addresses and author contributions are available at www.annals.org.

References

1. **Kaplan N.** J-curve not burned off by HOT study. Hypertension Optimal Treatment. Lancet. 1998;351:1748-9. [PMID: 9635941]
2. **Grossman E.** Does the 'J-curve' still hold in the post 'HOT' era? J Hum Hypertens. 1998;12:729-30. [PMID: 9844940]
3. **Weinberger MH.** Do no harm. Antihypertensive therapy and the 'J' curve [Editorial]. Arch Intern Med. 1992;152:473-6. [PMID: 1546907]
4. **Staessen JA.** Potential adverse effects of blood pressure lowering—J-curve revisited. Lancet. 1996;348:696-7. [PMID: 8806284]
5. **Cruickshank JM.** The J curve lives [Letter]. Lancet. 1992;339:187. [PMID: 1346046]
6. Coronary flow reserve and the J curve [Letter]. BMJ. 1988;297:1606-8. [PMID: 3147093]
7. **Cruickshank JM, Thorp JM, Zacharias FJ.** Benefits and potential harm of lowering high blood pressure. Lancet. 1987;1:581-4. [PMID: 2881129]
8. **Stewart IM.** Relation of reduction in pressure to first myocardial infarction in patients receiving treatment for severe hypertension. Lancet. 1979;1:861-5. [PMID: 86103]
9. **Fletcher A, Beevers DG, Bulpitt C, Butler A, Coles EC, Hunt D, et al.** Beta adrenoceptor blockade is associated with increased survival in male but not female hypertensive patients: a report from the DHSS Hypertension Care Computing Project (DHCCP). J Hum Hypertens. 1988;2:219-27. [PMID: 2907053]
10. **Samuelsson O, Wilhelmsen L, Andersson OK, Pennert K, Berglund G.** Cardiovascular morbidity in relation to change in blood pressure and serum cholesterol levels in treated hypertension. Results from the primary prevention trial in Göteborg, Sweden. JAMA. 1987;258:1768-76. [PMID: 3625987]
11. **Waller PC, Isles CG, Lever AF, Murray GD, McInnes GT.** Does therapeutic reduction of diastolic blood pressure cause death from coronary heart disease? J Hum Hypertens. 1988;2:7-10. [PMID: 3236316]
12. Cardiovascular risk and risk factors in a randomized trial of treatment based on the beta-blocker oxprenolol: The International Prospective Primary Prevention Study in Hypertension (IPPPSH). The IPPPSH Collaborative Group. J Hypertens. 1985;3:379-92. [PMID: 2864374]
13. **Coope J, Warrender TS.** Randomised trial of treatment of hypertension in elderly patients in primary care. Br Med J (Clin Res Ed). 1986;293:1145-51. [PMID: 3094811]
14. **Farnett L, Mulrow CD, Linn WD, Lucey CR, Tuley MR.** The J-curve phenomenon and the treatment of hypertension. Is there a point beyond which pressure reduction is dangerous? JAMA. 1991;265:489-95. [PMID: 1824642]
15. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Arch Intern Med. 1997;157:2413-46. [PMID: 9385294]
16. **Bots ML, Witteman JC, Hofman A, de Jong PT, Grobbee DE.** Low diastolic blood pressure and atherosclerosis in elderly subjects. The Rotterdam study. Arch Intern Med. 1996;156:843-8. [PMID: 8774202]
17. **Vatten LJ, Holmen J, Krüger O, Forsén L, Tverdal A.** Low blood pressure and mortality in the elderly: a 6-year follow-up of 18,022 Norwegian men and women age 65 years and older. Epidemiology. 1995;6:70-3. [PMID: 7888450]
18. **Glynn RJ, Chae CU, Guralnik JM, Taylor JO, Hennekens CH.** Pulse pressure and mortality in older people. Arch Intern Med. 2000;160:2765-72. [PMID: 11025786]
19. **Pastor-Barriuso R, Banegas JR, Damián J, Appel LJ, Guallar E.** Systolic blood pressure, diastolic blood pressure, and pulse pressure: an evaluation of their joint effect on mortality. Ann Intern Med. 2003;139:731-9. [PMID: 14597457]
20. **van den Hoogen PC, van Popele NM, Feskens EJ, van der Kuip DA, Grobbee DE, Hofman A, et al.** Blood pressure and risk of myocardial infarction in elderly men and women: the Rotterdam study. J Hypertens. 1999;17:1373-8. [PMID: 10526896]
21. **Boshuizen HC, Izaks GJ, van Buuren S, Ligthart GJ.** Blood pressure and mortality in elderly people aged 85 and older: community based study. BMJ. 1998;316:1780-4. [PMID: 9624064]
22. **Witteman JC, Grobbee DE, Valkenburg HA, van Hemert AM, Stijnen T, Burger H, et al.** J-shaped relation between change in diastolic blood pressure and progression of aortic atherosclerosis. Lancet. 1994;343:504-7. [PMID: 7906758]
23. **Benetos A, Rudnichi A, Safar M, Guize L.** Pulse pressure and cardiovascular mortality in normotensive and hypertensive subjects. Hypertension. 1998;32:560-4. [PMID: 9740626]
24. **Floras JS.** Antihypertensive treatment, myocardial infarction, and nocturnal myocardial ischaemia. Lancet. 1988;2:994-6. [PMID: 2902496]
25. **Hakala SM, Tilvis RS, Strandberg TE.** Blood pressure and mortality in an older population. A 5-year follow-up of the Helsinki Ageing Study. Eur Heart J. 1997;18:1019-23. [PMID: 9183596]
26. **Benetos A, Thomas F, Bean K, Gautier S, Smulyan H, Guize L.** Prognostic

value of systolic and diastolic blood pressure in treated hypertensive men. Arch Intern Med. 2002;162:577-81. [PMID: 11871926]
27. **Tuomilehto J, Ryynänen OP, Koistinen A, Rastenyte D, Nissinen A, Puska P.** Low diastolic blood pressure and mortality in a population-based cohort of 16913 hypertensive patients in North Karelia, Finland. J Hypertens. 1998;16: 1235-42. [PMID: 9746108]
28. **Barrett-Connor E, Palinkas LA.** Low blood pressure and depression in older men: a population based study. BMJ. 1994;308:446-9. [PMID: 8124175]
29. **Zanchetti A, Hansson L, Clement D, Elmfeldt D, Julius S, Rosenthal T, et al.** Benefits and risks of more intensive blood pressure lowering in hypertensive patients of the HOT study with different risk profiles: does a J-shaped curve exist in smokers? J Hypertens. 2003;21:797-804. [PMID: 12658027]
30. **Staessen JA, Wang JG, Thijs L.** Cardiovascular prevention and blood pressure reduction: a quantitative overview updated until 1 March 2003. J Hypertens. 2003;21:1055-76. [PMID: 12777939]
31. **Nissen SE, Tuzcu EM, Libby P, Thompson PD, Ghali M, Garza D, et al.** Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. JAMA. 2004;292:2217-25. [PMID: 15536108]
32. **Pepine CJ.** What is the optimal blood pressure and drug therapy for patients with coronary artery disease? [Editorial] JAMA. 2004;292:2271-3. [PMID: 15536116]
33. **Pepine CJ, Handberg EM, Cooper-DeHoff RM, Marks RG, Kowey P, Messerli FH, et al.** A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. JAMA. 2003;290:2805-16. [PMID: 14657064]
34. INVEST overview. Accessed at www.medicine.ufl.edu/cardio/research /invest_info/invest_definitions.shtml on 25 April 2005.
35. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA. 2002;288:2981-97. [PMID: 12479763]
36. **Yusuf S, Wittes J, Friedman L.** Overview of results of randomized clinical trials in heart disease. I. Treatments following myocardial infarction. JAMA. 1988;260:2088-93. [PMID: 2901501]
37. **Pepine CJ.** Use of calcium antagonists in post-myocardial infarction patients [Editorial]. J Am Coll Cardiol. 1998;31:118-9. [PMID: 9426028]
38. **Pepine CJ, Faich G, Makuch R.** Verapamil use in patients with cardiovascular disease: an overview of randomized trials. Clin Cardiol. 1998;21:633-41. [PMID: 9755379]
39. **Yusuf S, Held P, Furberg C.** Update of effects of calcium antagonists in myocardial infarction or angina in light of the second Danish Verapamil Infarction Trial (DAVIT-II) and other recent studies [Editorial]. Am J Cardiol. 1991; 67:1295-7. [PMID: 2035457]
40. **Gibson RS, Hansen JF, Messerli F, Schechtman KB, Boden WE.** Long-term effects of diltiazem and verapamil on mortality and cardiac events in non-Q-wave acute myocardial infarction without pulmonary congestion: post hoc subset analysis of the multicenter diltiazem postinfarction trial and the second Danish Verapamil Infarction Trial studies. Am J Cardiol. 2000;86:275-9. [PMID: 10922432]
41. **Messerli FH, Hansen JF, Gibson RS, Schechtman KB, Boden WE.** Heart rate-lowering calcium antagonists in hypertensive post-myocardial infarction patients. J Hypertens. 2001;19:977-82. [PMID: 11393682]
42. **Owens P, O'Brien E.** Hypotension in patients with coronary disease: can profound hypotensive events cause myocardial ischaemic events? Heart. 1999;82: 477-81. [PMID: 10490564]
43. **Kannel WB, Wilson PW, Nam BH, D'Agostino RB, Li J.** A likely explanation for the J-curve of blood pressure cardiovascular risk. Am J Cardiol. 2004; 94:380-4. [PMID: 15276113]
44. **Messerli FH, Franklin S, Mancia G, Hewkin A, Kupfer S, Pepine CJ.** Increased pulse pressure is strongly associated with adverse cardiovascular outcomes: The International Verapamil SR-Trandolapril Study (INVEST) [Abstract]. Accessed at www.abstractsonline.com/arch/RecordView.aspx ?LookupKey=12345&recordID=2384 on 1 February 2006.
45. **Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, et al.** Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet. 1998;351:1755-62. [PMID: 9635947]
46. **Greenberg JA.** Removing confounders from the relationship between mortality risk and systolic blood pressure at low and moderately increased systolic blood pressure. J Hypertens. 2003;21:49-56. [PMID: 12544435]
47. **Berl T, Hunsicker LG, Lewis JB, Pfeffer MA, Porush JG, Rouleau JL, et al.** Impact of achieved blood pressure on cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial. J Am Soc Nephrol. 2005;16:2170-9. [PMID: 15930097]
48. **Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al.** The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003;289:2560-72. [PMID: 12748199]

Current Author Addresses: Dr. Messerli: Division of Cardiology, St. Luke's-Roosevelt Hospital, 1000 Tenth Avenue, New York, NY 10019.
Dr. Mancia: Dipartimento di Medicina Clinica, Università degli Studi di Milano–Bicocca, Ospedale San Gerardo di Monza, Via Donizetti 106, 20052 Monza, Milan, Italy.
Drs. Conti and Pepine: Division of Cardiovascular Medicine, 1600 SW Archer Road, Box 100277, Gainesville, FL 32610-0277.
Ms. Hewkin: DR435, AP9A, Abbott, 200 Abbott Park Road, Abbott Park, IL 60045.
Dr. Kupfer: 640 Colwyn Terrace, Deerfield, IL 60015.
Ms. Champion: DR439, AP30-3, Abbott, 200 Abbott Park Road, Abbott Park, IL 60045-6145.
Dr. Kolloch: Gilead Medical Center, University of Munster, Munster, Germany.
Dr. Benetos: Centre de Geriatrie, Hôpital Brabois, University of Nancy, 54511 Nancy-les-Vandoeuvre, France.

Author Contributions: Conception and design: F.H. Messerli, G. Mancia, S. Kupfer, R. Kolloch, C.J. Pepine.
Analysis and interpretation of the data: F.H. Messerli, G. Mancia, C.R. Conti, A.C. Hewkin, S. Kupfer, A. Champion, R. Kolloch, A. Benetos, C.J. Pepine.
Drafting of the article: F.H. Messerli, G. Mancia, A.C. Hewkin, S. Kupfer, R. Kolloch, A. Benetos, C.J. Pepine.
Critical revision of the article for important intellectual content: F.H. Messerli, G. Mancia, C.R. Conti, S. Kupfer, A. Champion, R. Kolloch, A. Benetos, C.J. Pepine.
Final approval of the article: F.H. Messerli, G. Mancia, C.R. Conti, R. Kolloch, A. Benetos, C.J. Pepine.
Provision of study materials or patients: F.H. Messerli, C.R. Conti, C.J. Pepine.
Statistical expertise: F.H. Messerli, A.C. Hewkin.
Obtaining of funding: C.J. Pepine.
Administrative, technical, or logistic support: C.J. Pepine.
Collection and assembly of data: F.H. Messerli, C.J. Pepine.