Antihypertensive Treatment Alters the Predictive Strength of Pulse Pressure and Other Blood Pressure Measures

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**Background:** The objective of this study was to assess whether antihypertensive treatment affects the predictive power of brachial pulse pressure.

**Methods:** Data from the First National Health and Nutrition Examination Survey Epidemiologic Follow Up Study were used to conduct Cox regression analyses. There were 487 cardiovascular disease (CVD) and 348 coronary heart disease (CHD) deaths during an 8.6-year follow-up among 2939 hypertensive subjects 33 to 87 years of age. A correction was made for the regression–dilution bias.

**Results:** Pulse pressure (PP) was a significant single predictor for treated, but not untreated, hypertensive subjects. The hazard ratio (95% confidence interval) for CVD mortality for an 10–mm Hg increment of PP was 1.16 (95% CI = 1.08 to 1.25) for treated hypertensive subjects, and 1.12 (95% CI = 0.99 to 1.26) for untreated hypertensive subjects. Also, PP was a significant predictor after accounting for the effects of mean arterial pressure (MAP), but only in treated hypertensive subjects. The pattern was opposite for diastolic pressure (DBP). Analysis of antihypertensive treatment trends suggests that clinicians focused treatment more on hypertensive subjects with elevated DBP and low PP during the 1970s and early 1980s, thereby causing DBP to become a weak predictor and PP a strong predictor among treated hypertensive subjects. This tendency was particularly noticeable at higher ages. For instance, among hypertensive subjects ≥65 years of age during this period, the percentage who were treated increased from 7.6% to 45.0%, and the ratio of subjects with isolated systolic hypertension to those with isolated diastolic hypertension among those who were untreated increased from 11.2 to 45.1.

**Conclusions:** The findings of this prospective study suggest that antihypertensive treatment can alter the predictive strength of PP and other blood pressure measures. Am J Hypertens 2005;18:1033–1039 © 2005 American Journal of Hypertension, Ltd.

**Key Words:** Pulse pressure, cardiovascular disease, mortality prognosticators, hypertension, antihypertensive treatment.

T here have been conflicting reports about the relative predictive strength of auscultatory office brachial pulse pressure (PP). Some investigators have concluded that PP is a better predictor than diastolic blood pressure (DBP), systolic blood pressure (SBP), and mean arterial pressure (MAP). Others have found the opposite.

Part of the conflict may be caused by different types of antihypertensive treatment among subjects in these previous studies, because antihypertensive treatment itself could affect the predictive strength of PP. For instance, recommendations from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) during the 1970s and 1980s focused primarily on elevated DBP. Antihypertensive treatment focused on elevated DBP could decrease DBP more than SBP among hypertensive subjects in prospective follow-up studies. This treatment strategy would tend to reduce elevated DBP more than elevated SBP and hence increase PP among hypertensive subjects, and therefore increase the predictive strength of PP.

The purpose of the present analysis was to assess the effects of antihypertensive treatment in the 1970s and 1980s on the predictive strength of different auscultatory office brachial blood pressure (BP) measures among hypertensive subjects in the First National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow up Study (NHEFS).
Methods

The NHEFS is a longitudinal study of the persons 25 to 74 years of age \((N = 14,407)\) examined in 1971–1975 in NHANES I, a probability sample survey of the noninstitutionalized civilian population in the United States.\(^{12}\) Four follow-up surveys have been completed in NHEFS, in 1982–1984, 1986, 1987, and 1992. The baseline data used in the present study were obtained by means of medical histories and examinations and by survey questionnaires administered at the 1971–1975 survey and at the first follow-up survey in 1982–1984.\(^{13}\)

The 1982–1984 survey was used as follow-up baseline data in all survival analyses. After excluding subjects with any missing data, there were 2939 subjects between 33 and 87 years of age in the 1982–1984 survey, and 487 CVD and 348 CHD deaths that occurred during the subsequent follow-up, which lasted an average of 8.6 years for censored subjects. The mortality data in the study were obtained from tracing activities conducted at the 1986, 1987, and 1992 follow-up surveys. Each death was confirmed either by death certificate or proxy interview. Death certificates were obtained for \(>95\%\) of deceased subjects.\(^{14}\)

A single sphygmomanometric brachial BP measurement was made by a physician in the 1971–1975 survey,\(^{12}\) and three such BP measurements were made by a trained nonphysician interviewer in the 1982–1984 survey.\(^{13}\) The single 1971–1975 measurement and the average of the second and third 1982–1984 measurements were used in the present analysis.

Data from the 1971–1975 survey and the 1982–1984 survey were used to define and classify hypertensive subjects. Treated hypertensive subjects were subjects who reported taking antihypertensive medication. Untreated hypertensive subjects were subjects who reported that they were not taking antihypertensive medication, and who had DBP \(\geq 90\) or SBP \(\geq 140\). These classifications were made separately for each survey using data collected in the survey.

Subjects were considered to have a history of CVD or diabetes if they responded in the affirmative to a question presented during the 1982–1984 survey and asking whether a physician had told them they had the condition.

Cox proportional hazards regression\(^{15}\) was used to calculate multivariate hazard ratios (HRs) for a 10–mm Hg increment in each BP measure. Cumulative hazard and log-minus-log plots provided no evidence against proportionality assumptions.\(^{16}\) The \(-2\) log likelihood \((-2LL)\) test was used to compare the fit of alternative models. Four BP measures were tested for predictive strength: DBP, SBP, PP, and MAP. The PP was the difference between SBP and DBP, and MAP was DBP plus one third of PP. To correct for the regression–dilution bias,\(^8\) survival analyses were performed using each subject’s usual BP as predictor. The average of the BP measurements in the 1971–1975 and 1982–1984 surveys was used as an estimate of the usual BP, as this measure has been shown to mitigate regression–dilution effects.\(^7\)

Two criteria were used to assess the predictive strength of a BP measure: 1) whether the measure made a significant contribution relative to the other predictor in a two-predictor model; and 2) whether the measure was a significant single predictor.

The following covariates were used in all survival analyses: gender; ethnicity; educational level; per capita income; smoking (five categories); alcohol consumption (four categories); physical activity (five categories); and age (eleven 5-year categories); history of CVD (yes/no); history of diabetes (yes/no); and body mass index (BMI, in kg/m\(^2\); six categories). The BMI was calculated as body weight measured in 1982–1984, in kilograms, divided by the square of height measured in 1971–1975, in meters.

The ratio of the number of untreated subjects with isolated systolic hypertension (ISH) to the number of untreated subjects with isolated diastolic hypertension (IDH) was used as a crude measure of how intensively physicians focused antihypertensive treatment more on elevated DBP than on elevated SBP. The rationale was that if physicians preferred to treat patients with elevated DBP rather than elevated SBP, the ratio would increase among the untreated hypertensive subjects and vice versa.

Results

Table 1 shows that at follow-up baseline, treated hypertensive subjects were more likely than untreated hypertensive subjects to be female, nonsmokers, and alcohol abstainers, and to have high BMI and a history of acute myocardial infarction, stroke, angina, and diabetes.

Effects of Treatment on Relative Predictive Strengths of PP and DBP

Pulse pressure was found to be a strong predictor among treated but not untreated hypertensive subjects. First, PP was a stronger predictor than MAP only for treated hypertensive subjects (Table 2). For treated hypertensive subjects, the model containing PP and MAP was significantly better than the model containing only MAP \((-2LL = 6.82, \text{ } P = .009)\) but not better than the model containing only PP \((-2LL = 1.48, \text{ } P = .115)\). For untreated hypertensive subjects, the model containing PP and MAP was significantly better than the model containing only PP \((-2LL = 11.15, \text{ } P = .001)\), but not than the model containing only MAP \((-2LL = 0.82, \text{ } P = .365)\). Second, PP was a significant single predictor only for treated hypertensive subjects. The single-predictor HR (95% confidence interval [CI]) for CVD mortality, for a 10–mm Hg increment in PP, was 1.16 (95% CI = 1.08 to 1.25) for treated hypertensive subjects and 1.12 (95% CI = 0.99 to 1.26) for untreated hypertensive subjects.

Diastolic blood pressure was a strong predictor only among untreated hypertensive subjects. DBP was a significant single predictor only for untreated hypertensive sub-
The HR (95% CI) for CVD mortality for a 10–mm Hg increment in PP was 1.29 (95% CI = 1.09 to 1.52) for untreated hypertensive subjects and 1.11 (95% CI = 0.97 to 1.26) for treated hypertensive subjects. The two-model analyses showed that DBP was a weaker predictor than SBP for both treated and untreated hypertensive subjects.

Possible Causal Mechanism 1: Advanced Ischemic Heart Disease

Clinicians may have been more likely to treat hypertensive subjects with advanced ischemic heart disease and therefore stiffer arteries and higher PP, thereby causing PP to be a strong predictor among treated hypertensive subjects. To test this idea, the survival analyses in Table 2 were repeated for a subgroup of hypertensive subjects likely to have higher levels of ischemic heart disease and PP, namely, elderly hypertensive subjects with a history of CVD. Pulse pressure was found to be a strong predictor only in the treated group. The same pattern was found as for all hypertensive subjects combined. Mean arterial pressure was a stronger predictor than PP only in the untreated group. For untreated elderly hypertensive subjects with a history of CVD, the model containing PP and MAP was significantly better than the model containing only PP (−2LL = 5.76, P = .016), but not better than the model containing only MAP (−2LL = 0.07, P = .788). In the treated group, the model containing PP and MAP was not significantly better than the model containing only PP (−2LL = 3.45, P = .063) or better than the model containing only MAP (−2LL = 1.01, P = .315). Also, PP was not a significant single predictor for untreated elderly hypertensive subjects with a history of CVD. The single-predictor HR (95% CI) for CVD mortality was 1.16 (95% CI = 0.96 to 1.47) in the treated group (N = 293, deaths = 127).

Conversely, DBP was found to be a strong predictor only in the untreated group for elderly hypertensive subjects with a history of CVD. It was observed that DBP was only a significant single predictor in the untreated group. The HR (95% CI) for CVD mortality being 1.68 (95% CI = 1.01 to 2.80) in the untreated group (N = 123, deaths = 48) and 1.19 (95% CI = 0.96 to 1.47) in the treated group (N = 293, deaths = 127). The two-model analyses showed that DBP was a weaker predictor than SBP in both the treated and untreated groups.

Possible Causal Mechanism 2: Antihypertensive Treatment Itself

Clinicians may have focused antihypertensive treatment more on hypertensive subjects with elevated DBP than on those with elevated SBP. Elevated DBP is associated with low PP, and elevated SBP is associated with high PP. This treatment strategy would tend to reduce risk primarily for hypertensive subjects with elevated DBP and low PP, thereby preventing DBP from being a strong predictor for treated hypertensive subjects and causing PP to be a strong predictor for treated hypertensive subjects. Figure 1 shows that the ratio of ISH to IDH among all untreated hyper-

Table 1. Baseline characteristics of treated hypertensives and untreated hypertensives

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treated Hypertensives (N = 1695)</th>
<th>Untreated Hypertensives (N = 1244)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>65.3 (0.3)*</td>
<td>63.8 (0.4)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>34.7†</td>
<td>47.7</td>
</tr>
<tr>
<td>Per capita income ($000)</td>
<td>8.21 (0.52)</td>
<td>8.26 (0.70)</td>
</tr>
<tr>
<td>Educational level‡</td>
<td>32.7 (0.4)</td>
<td>32.8 (0.6)</td>
</tr>
<tr>
<td>Currently smoking (%)</td>
<td>27.6†</td>
<td>30.6</td>
</tr>
<tr>
<td>Alcohol ≥1 drink/day (%)</td>
<td>30.2†</td>
<td>38.4</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.5 (0.3)†</td>
<td>26.3 (0.5)</td>
</tr>
<tr>
<td>History of acute myocardial infarction (%)</td>
<td>8.7†</td>
<td>3.9</td>
</tr>
<tr>
<td>History of stroke (%)</td>
<td>2.5†</td>
<td>0.7</td>
</tr>
<tr>
<td>History of angina (%)</td>
<td>16.7†</td>
<td>7.9</td>
</tr>
<tr>
<td>History of diabetes (%)</td>
<td>12.9†</td>
<td>7.3</td>
</tr>
<tr>
<td>Usual DBP (mm Hg)</td>
<td>85.3 (0.6)</td>
<td>84.9 (0.8)</td>
</tr>
<tr>
<td>Usual SBP (mm Hg)</td>
<td>142.4 (1.0)</td>
<td>143.5 (1.4)</td>
</tr>
<tr>
<td>Usual MAP (mm Hg)</td>
<td>104.4 (0.6)</td>
<td>104.4 (0.9)</td>
</tr>
<tr>
<td>Usual PP (mm Hg)</td>
<td>57.1 (0.9)</td>
<td>58.7 (1.2)</td>
</tr>
</tbody>
</table>

BMI = body mass index; DBP = diastolic blood pressure; MAP = mean arterial pressure; PP = pulse pressure.

Number in parentheses are SEM. Treated hypertensives were subjects who reported taking antihypertensive medication in the 1982–1984 survey. Untreated hypertensives were subjects who reported not taking antihypertensive medication, and with DBP ≥90 or SBP ≥140 in the 1982–1984 survey.

All characteristics except age and gender were adjusted for age in 5-year intervals. Dichotomous variables were age adjusted using the direct method with all hypertensive subjects in the survival analyses used as the reference population.

* P < .01; † P < .001 for difference between the two groups, by t test for age and BMI; by ANOVA after adjusting for age in 5-year categories for other continuous variables, by χ² for dichotomous variables.

‡ Educational level was an ordinal variable with 35 levels.
The survival analyses in Table 2 yielded essentially the same patterns of HR variations, but with wider 95% CIs because of the smaller sample size. When the analyses were repeated separately for men and women, there were some minor differences. For instance, for women aged >65 years, the HR for PP was a significant single predictor for treated but not for untreated hypertensive subjects. Also, the one-predictor HR for PP was more obviously greater for treated than for untreated hypertensive subjects. The HR (95% CI) for mand patients was 0.95 (0.82–1.10) and 1.10 (0.98–1.23) for treated and untreated hypertensive subjects, respectively.

### Secondary Analyses

The one-predictor HRs for DBP were 1.20 (1.08–1.32) and 1.29 (1.09–1.52) for all hypertensive subjects and untreated hypertensive subjects, respectively. The one-predictor HRs for SBP were 1.17 (1.11–1.23) and 1.21 (1.09–1.34) for all hypertensive subjects and untreated hypertensive subjects, respectively. The one-predictor HRs for MAP were 1.28 (1.17–1.40) and 1.36 (1.16–1.60) for all hypertensive subjects and untreated hypertensive subjects, respectively. The one-predictor HRs for PP were 1.15 (1.08–1.22) and 1.12 (0.99–1.26) for all hypertensive subjects and untreated hypertensive subjects, respectively.

### Table 2. Hazard ratio (95% confidence interval) for cardiovascular disease (CVD) mortality, for a 10-mm Hg increment in blood pressure (BP)

<table>
<thead>
<tr>
<th>Subjects</th>
<th>N</th>
<th>Deaths</th>
<th>DBP</th>
<th>SBP</th>
<th>MAP</th>
<th>PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>All hypertensive subjects</td>
<td>2937</td>
<td>486</td>
<td>1.20 (1.08–1.32)*</td>
<td>1.17 (1.11–1.23)†</td>
<td>1.28 (1.17–1.40)†</td>
<td>1.15 (1.08–1.22)†</td>
</tr>
<tr>
<td>Treated hypertensive subjects</td>
<td>1694</td>
<td>305</td>
<td>1.11 (0.97–1.26)</td>
<td>1.15 (1.08–1.22)†</td>
<td>1.21 (1.08–1.36)*</td>
<td>1.16 (1.08–1.25)†</td>
</tr>
<tr>
<td>Untreated hypertensive subjects</td>
<td>1243</td>
<td>181</td>
<td>1.29 (1.09–1.52)*</td>
<td>1.21 (1.09–1.34)†</td>
<td>1.36 (1.16–1.60)†</td>
<td>1.12 (0.99–1.26)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subjects</th>
<th>N</th>
<th>Deaths</th>
<th>Diastolic BP and Systolic BP</th>
<th>MAP and PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>All hypertensive subjects</td>
<td>2937</td>
<td>486</td>
<td>1.05 (0.94–1.17) and 1.16 (1.09–1.23)†</td>
<td>1.21 (1.10–1.34)† and 1.09 (1.01–1.16)†</td>
</tr>
<tr>
<td>Treated hypertensive subjects</td>
<td>1694</td>
<td>305</td>
<td>0.96 (0.83–1.11) and 1.16 (1.08–1.25)†</td>
<td>1.11 (0.98–1.27) and 1.12 (1.03–1.22)*</td>
</tr>
<tr>
<td>Untreated hypertensive subjects</td>
<td>1243</td>
<td>181</td>
<td>1.14 (0.95–1.38) and 1.17 (1.03–1.31)†</td>
<td>1.33 (1.13–1.57)* and 1.06 (0.94–1.20)</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.

Hazard ratios were adjusted for BMI, history of diabetes, history of CVD, age, gender, ethnicity, per-capita income, educational level, physical activity, smoking status, and alcohol consumption, as described in Methods. Hypertensives were subjects with measured DBP ≥90 mm Hg or SBP ≥140 mm Hg, or taking antihypertensive medications in the 1982–1984 survey. Treated hypertensives were subjects who reported using antihypertensive medication in the 1982–1984 survey. Untreated hypertensives were subjects who reported not taking antihypertensive medication, and with DBP ≥90 or SBP ≥140 in the 1982–1984 survey.

* P < .01; † P < .001; ‡ P < .05.

### FIG. 1

The ratio of number of untreated hypertensive subjects with isolated systolic hypertension (ISH) to the number with isolated diastolic hypertension (IDH) and the level of treatment. The ratio of ISH to IDH among untreated ≥65-year-old hypertensive subjects increased from 11.2 to 45.1 (Fig. 1).
hypertensive subjects for CVD mortality, for a 10–mm Hg increment in PP, was 1.50 (95% CI = 1.17 to 1.94) for treated subjects and 0.97 (95% CI = 0.65 to 1.44) for untreated subjects.

The survival analyses were repeated using the definition of hypertension in the JNC guidelines in effect in the 1970s and early 1980s (ie, DBP ≥90 mm Hg). The results were essentially the same as those in Table 2, except that DBP was a stronger predictor than SBP in the two-predictor model for untreated hypertensive subjects. In this model, the HR (95% CI) was 2.22 (95% CI = 1.35 to 3.66) and 1.03 (95% CI = 0.80 to 1.33) for DBP and SBP, respectively.

**Discussion**

The main findings in the present prospective analysis using a sample of the US population from the early 1980s is that auscultatory office brachial PP was a strong predictor of CVD risk for treated but not untreated hypertensive subjects, and that the opposite was true for DBP. It was based on a relatively large number of events, and was found for the following: 1) both nonelderly and elderly hypertensive subjects, CVD and CHD mortality, and male and female hypertensive subjects; 2) elderly hypertensive subjects with a history of CVD; 3) whether or not the treated hypertension was controlled; and 4) whether the current definition of hypertension or that in effect in the 1970s and early 1980s (ie, DBP ≥90 mm Hg). The results were essentially the same as those in Table 2, except that DBP was a stronger predictor than SBP in the two-predictor model for untreated hypertensive subjects. In this model, the HR (95% CI) was 2.22 (95% CI = 1.35 to 3.66) and 1.03 (95% CI = 0.80 to 1.33) for DBP and SBP, respectively.

The present study appears to be the first to focus on differences between the predictive strength of PP for treated and untreated hypertensive subjects. The present findings cannot be meaningfully compared with most previous studies because they did not include separate analyses for hypertensive subjects or did not distinguish between treated and untreated hypertensive subjects. A few previous investigators did, however, assess the predictive strength of PP among either treated or untreated hypertensive subjects. Two studies found PP to be a strong predictor among treated hypertensive subjects, as was found here. Another study did not; however its end point was congestive heart failure, not CVD or CHD mortality, and this difference in end points may account for the conflicting findings. Four other studies addressed the same question in antihypertensive treatment programs. They found that PP upon entry into treatment was a strong predictor of CVD risk during treatment. Their finding disagrees with the present finding that PP was not a strong predictor for untreated hypertensive subjects. This disagreement may be caused by an increase in the predictive strength of their pretreatment PP caused by the treatment during their follow-up, because only a minority of hypertensive subjects in NHEFS were receiving treatment during follow-up in the present analysis (Fig. 1). One of these groups found that PP was also a strong predictor in its placebo control group, and this may be because their entry criteria constrained DBP but not SBP.

The causal mechanism that seemed to be best at explaining how treatment could cause PP to become a strong predictor is that clinicians were more likely to use aggressive treatment approaches in their hypertensive patients with elevated DBP and low PP, and thus to reduce risk more among treated hypertensive subjects with elevated DBP and low PP. Several lines of evidence support this idea. First, it was found that clinicians appeared to be more likely to select NHEFS hypertensive subjects with IDH than those with ISH for treatment. In other words they were probably selecting for treatment hypertensive subjects with elevated DBP and lower PP more than those with elevated SBP and higher PP. Second, this treatment selection pattern is consistent with guidelines in the 1970s and 1980s, such as those from JNC, which used only DBP as the basis for diagnosis and treatment decisions.
SBP was a significant single predictor for both treated and untreated hypertensive subjects. This latter finding agrees with the conclusion by Benetos et al., in their study of 4714 hypertensive Parisian individuals whose BP was measured in the 1970s and 1980s, that more aggressive treatment in hypertensive subjects with elevated DBP than in those with elevated SBP could have decreased the predictive strength of DBP relative to that of SBP.

One other possible causal mechanism was assessed and found not to be convincing. This mechanism was based on findings in the 1980s, such as the one by Safar et al. These investigators found that in systolic–diastolic hypertensive subjects for whom antihypertensive treatment decreased DBP but not SBP and hence increased PP, arteries exhibited rigidity that apparently resulted from alterations in the arterial wall. Conversely they found that if the treatment decreased both DBP and SBP, and hence did not increase PP, arterial rigidity was lower. Therefore the present second mechanism proposed that clinicians were more likely to select hypertensive subjects with advanced ischemic heart disease for antihypertensive treatment. Treated hypertensive subjects would thus be more likely than untreated hypertensive subjects to have advanced ischemic heart disease, and therefore stiff arteries and high PP, low DBP, and high CVD risk, causing PP to be a strong predictor of CVD risk, and the opposite for DBP. However, in the present analysis, PP was not, and DBP was, a strong predictor for elderly untreated hypertensive subjects with a history of CVD; and PP was, and DBP was not, a strong predictor for elderly treated hypertensive subjects with a history of CVD. This result does not argue against further research on new drugs aimed specifically at reducing PP. On the contrary, such research seems warranted, because: 1) there is some evidence suggesting that traditional antihypertensive drugs are more effective in decreasing CVD mortality if the drug-induced decreases in BP are accompanied by decreases in arterial stiffness; and 2) there are drugs that have demonstrated an ability to decrease both PP and arterial stiffness.

In 1993, for the first time, the JNC used both SBP and DBP in its guidelines for classifying and treating hypertension. This change was based on studies conducted mostly in the 1980s and early 1990s that showed that SBP is important in assessing both risk and treatment outcomes. The present findings do suggest, therefore, that future survival analyses of the relative predictive strength of different BP measures among treated hypertensive subjects may arrive at conclusions differing from those found here. Treatment that focuses on both elevated SBP and elevated DBP could actually decrease the predictive strength of PP. The finding by Psaty et al. that SBP was the strongest predictor of acute myocardial infarction incidence for treated elderly hypertensive subjects is consistent with this idea, because the baseline survey by Psaty et al. occurred between 1989 and 1993 and their follow-up averaged 6.7 years.

One of the limitations of the present analysis is that it did not adjust for the nonrandom sampling techniques used in the NHANES, so that the present results cannot be generalized with confidence to the US population.

In conclusion, this prospective analysis suggests that antihypertensive treatment can alter the predictive strength of PP and other BP measures.

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