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Blood Pressure Indices and Cardiovascular Disease in the Asia Pacific Region

A Pooled Analysis

Asia Pacific Cohort Studies Collaboration

Abstract—This article aims to compare the importance of systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and pulse pressure (PP) as risk factors for stroke and ischemic heart disease and to assess whether the patterns are consistent by age and gender. Cox proportional-hazards regression, adjusted for cholesterol and smoking, was used to assess the associations of the 4 BP indices with stroke and ischemic heart disease by age and gender. The relative importance of individual indices was assessed with a hazard ratios for a 1-SD change in BP and by likelihood-ratio χ^2 tests. The influence of >1 BP index in the Cox model was also estimated. The analyses demonstrated similar associations of SBP, DBP, and MAP with both fatal stroke and ischemic heart diseases, which were stronger than those of PP. Both SBP and MAP tended to be more important in the regression model than DBP or PP. In Cox models including DBP, addition of SBP improved the goodness of fit at all ages and for both genders. However, in Cox models including SBP, addition of DBP typically resulted in little incremental benefit over and above that of SBP alone. These data suggest that if time or resources are highly constrained, such as in much-needed epidemiologic surveys in developing countries, very little is lost from only measuring SBP. (*Hypertension*. 2003;42:69-75.)

Key Words: blood pressure ■ cardiovascular diseases ■ epidemiology ■ meta-analysis

Blood pressure (BP) is an important risk factor for cardiovascular disease, and it is a key component of any formula that predicts cardiovascular risk.¹⁻⁴ However, uncertainties remain over which BP indices, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), or pulse pressure (PP), are the most important risk factors for a cardiovascular event.

In the past, greater emphasis was always placed on DBP than SBP, because elevation of the former variable was thought to confer greater risk for cardiovascular disease than elevated SBP.^{5,6} Data from the Framingham study, published >30 years ago, demonstrated that this was not the case,^{7,8} and most guidelines now include both indices.^{9,10} More recently, attention has also focused on the role of MAP and PP in cardiovascular disease,¹¹⁻¹⁵ and several analyses using different methodologies have explored the relative importance of all 4 BP indices. The majority of analyses have demonstrated that the association between SBP and cardiovascular disease is stronger than that of DBP in most age and gender groups.^{11-14, 16-18} Neither MAP nor PP has been shown to be conclusively superior to SBP.^{11,12,14,15,18,19} Data from a large number of cohort studies have demonstrated that the relative magnitude of the association between SBP and DBP and cardiovascular disease differs by

age.^{20,21} Several analyses have also suggested that the relative importance of BP indices may change with age and that DBP could be more important in those aged <50 years,^{14,18,22} but this finding is not consistent.^{13,16,17} Most analyses have not compared the BP indices by gender, and most have been based on North American or European populations.

Data from the Asia Pacific Cohort Studies Collaboration (APCSC) presented an ideal opportunity to compare all 4 BP indices for both fatal stroke and ischemic heart disease (IHD). This dataset has considerable follow-up data, which allowed analyses to assess whether the importance of BP indices varied by age, gender, and cardiovascular end point. Analyses of data from Asia, Australia, and New Zealand determined whether patterns in these populations were similar to those previously documented in predominantly European and North American studies. Secondary analyses were able to determine the influence of a combination of BP indices. This information will help clarify the relative importance of BP indices, and it also has the potential to contribute to better risk prediction.

Methods

Study Sample

The methods of study identification for the APCSC have been reported elsewhere.²³ In brief, prospective cohort studies were

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From the Asia Pacific Cohort Studies Collaboration.

The Writing Committee and members are listed in the Appendix.

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eligible for inclusion if they included study populations from the Asia Pacific region with at least 5000 person-years of follow-up recorded or planned. They had to have recorded data on date of birth or age, gender, BP at baseline, and age at death. Additional data sought included date of the baseline survey, total blood cholesterol, diabetes, height, weight, smoking habit, and any data on repeated measures of risk factors. Outcome data included stroke and IHD.²³ Data from a total of 37 cohort studies have been collated to date.

Statistical Methods

Primary analyses assessed the relation of individual BP indices to cardiovascular end points. MAP was calculated as $2/3$ DBP + $1/3$ SBP, and PP as SBP – DBP. The analyses were performed on “one-off” measures (ie, taken at one point in time only) of BP, which are appropriate in a clinical setting. They were not adjusted for regression dilution bias.²⁴ Because several different cohort studies were included, potential statistical heterogeneity was taken into account by stratifying by cohort. Additional effect modification was assessed with the use of statistical interaction terms for age and gender. When there was evidence of effect modification, analyses were stratified into the relevant subgroups. Cox proportional-hazards analyses²⁵ were then used to regress time until first event against baseline BP with individual participant data collected in all cohorts. Analyses were undertaken for total (fatal and nonfatal) and fatal events separately and were also performed separately for 2 end points: stroke and IHD. Fatal events were defined as death occurring within 28 days after the stroke or IHD event; additional data on disease end points has been published elsewhere.²³ Each BP index was considered separately as a continuous variable in the Cox regression. Regression coefficients and SEs were calculated with and without adjusting for cholesterol and smoking. Serum total cholesterol was fitted as a continuous variable (mmol/L), and smoking status was categorical (never vs ever smoked).

To compare the association of different BP indices with a particular end point, hazard ratios and 95% confidence intervals (CIs) were estimated for a 1-SD difference in each index. This is a “standardized” comparison of hazard ratios and is necessary because each BP index is measured on a different scale. The likelihood ratio χ^2 was used as a measure of the improvement of goodness of fit,²⁶ or “informativeness,” between a model containing each BP index (and the confounders smoking and cholesterol) compared with a model that only contained the confounders but no BP index (the “base model”) by age and gender.

Because some of the 37 cohorts in the collaboration included different age and gender subgroups, only a subset of cohorts is included in this report. This was done because one of the aims of the current analysis was to assess whether the relative importance of BP indices varied by age and gender. Comparisons of BP indices by using likelihood-ratio χ^2 across age and gender subgroups are valid only if the regression models for males, females, and different age groups are nested within each other. This means that they must be based on the same participants, and thus, restriction of studies was necessary. Inclusion of studies that did not contribute to all age-gender subgroups would have made age and gender comparisons invalid, because it would not have been possible to determine whether patterns with age and gender were real or artifactual due to missing data. In total, a subset of 16 cohort studies included participants of both genders with age groups ranging from <50 years to ≥ 70 years and with data on BP, cholesterol, and smoking status. Participants with complete data from these 16 studies were used for the purposes of these analyses.

Secondary analyses consisted of including 2 BP indices in the Cox proportional-hazards model to assess the relation simultaneously with adjustment for each other. The likelihood-ratio χ^2 test between the model containing a single BP index and the model containing >1 index was used to assess whether the additional index significantly improved the adequacy of the model. A significant likelihood-ratio χ^2 indicates that the regression coefficient of the additional index is significant compared with zero;^{26,27} ie, the index provides significantly more information. If the 2 BP indices are highly correlated, then collinearity might become a problem. When considering the

joint effects of SBP and DBP, we assessed collinearity by inspecting the changes in the coefficient and SE of SBP caused by the addition of DBP and vice versa. Large changes in either the parameter estimate or SE are indicative of collinearity.²⁸

Results

Study Sample

Data from 16 cohort studies, which included 94 147 participants and $>799\,000$ person-years of follow-up, were included in these analyses (Table 1). There were 3 cohorts from mainland China (13% of participants), 8 from Japan (17%), 1 from Taiwan (6%), 3 from Australia (61%), and 1 from New Zealand (3%). The mean age of participants at baseline was 52 years, and 54% of participants were female. During a mean follow-up of 8.5 years, a total of 1814 strokes (1120 fatal) and 1677 IHD events (1312 fatal) were recorded.

Investigating a Single BP Index

When the interaction terms for age and gender were introduced into the model, there were significant ($P < 0.05$) differences between some of these subgroups, suggesting that there was an effect modification by age and gender. This effect modification was also evident in previous BP analyses of all APCSC cohorts.²¹ Therefore, all further analyses were performed by age (classified as <50 , 50 to 59, 60 to 69, and ≥ 70 years) and gender. Analyses were carried out separately by country, and there were no consistent differences between countries. Country-specific results were also consistent with analyses of the overall group, which are presented in this article. (For example, in 60- to 69-year-old women, the association between BP and stroke was stronger for both SBP and MAP compared with DBP and PP across all countries.) In addition, separate analyses were performed that excluded participants who had a history of cardiovascular disease (for those studies that provided this information) and on several large APCSC cohorts excluded from the main analyses, and similar patterns were evident to those presented later. The difference between adjusted hazard ratios and those that were unadjusted for cholesterol and smoking was negligible, so adjusted analyses are presented.

Stroke

Analyses that were adjusted for cholesterol and smoking demonstrated that the association between each BP index and fatal stroke events was log-linear and positive and that the association was significant for most age and gender subgroups (Figure 1). The association between any given BP index and stroke was stronger in the youngest age groups; ie, the association was attenuated with age for males and females. The associations were similar in magnitude for all 4 BP indices within each subgroup; however, most frequently, the hazard ratios were highest for MAP and SBP, but the absolute differences were small. These patterns were also evident when analyses were performed on total stroke events.

The results of each BP index compared with the base model by age and gender subgroups are shown in Figure 1. Analyses demonstrated that in both males and females, SBP tended to be more informative than DBP (the only exception was in males aged <50 years). MAP ranked similarly to SBP in most age groups, and one or the other of these indices was

TABLE 1. Characteristics of the 16 APCSC Cohorts Used for Analyses to Compare BP Indices*

Region and Study Name	Start Year	Sample Size	Follow-Up, y	Female, %	Age at Baseline, y		Mean SBP	Mean DBP	Stroke Events		IHD Events	
					Mean	Range			Total	Fatal	Total	Fatal
Mainland China												
Huashan	1990	1801	2.8	52	53	35-75	126	76	16	6	3	3
Seven Cities Cohorts	1987	6362	5.7	57	58	35-91	134	83	220	123	61	61
Shanghai Factory Workers	1972	3966	13.9	5	50	30-78	126	79	138	138	50	50
Japan												
Aito Town	1980	1116	15.3	59	51	20-73	137	80	20	20	10	10
Hisayama	1961	1548	19.1	56	56	40-92	135	78	315	171	88	52
Konan	1987	1220	6.3	55	52	20-96	130	78	13	13	3	3
Miyama	1988	413	6.6	62	59	40-80	129	77	0	0	0	0
Ohasama	1992	1907	4.2	65	58	27-91	127	72	42	5	4	4
Saitama	1986	3615	9.6	62	55	20-94	135	80	55	55	24	24
Shibata	1977	2328	16.0	58	57	40-89	131	78	203	203	66	66
Shigaraki Town	1991	3722	3.9	59	57	29-95	132	78	13	13	3	3
Taiwan												
CVDFACTS	1988	5540	6.4	56	47	20-92	118	75	29	29	12	12
Australia												
Busselton	1966	7344	20.3	52	45	20-94	138	77	636	251	970	665
Melbourne	1990	41 141	5.7	59	55	27-75	138	77	32	32	161	161
Perth	1979	9729	12.5	47	45	20-90	130	81	59	59	186	186
New Zealand												
Fletcher Challenge	1992	2395	4.8	22	40	20-88	124	77	23	2	36	12
Total or overall		94 147	8.5	54	52	20-96	134	78	1814	1120	1677	1312
Weighted average**				52	51	26-86	134	78				

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; IHD, ischemic heart disease. Total person years of follow-up: 799 366.

*Only those APCSC studies and participants that had data on blood pressure, cholesterol, and smoking (defined as never and ever) and contained participants aged <50 and >70 years were included in these analyses. **Weighted average, weighting by person years of follow-up.

most informative in all of the age-gender subgroups for fatal stroke events and total stroke events, the only exception being males aged ≥70 years. In contrast, PP was typically less important than SBP.

Ischemic Heart Disease

Adjusted analyses demonstrated that in all age groups, the association between each of the BP indices and fatal IHD events was log-linear and positive, but it was not statistically

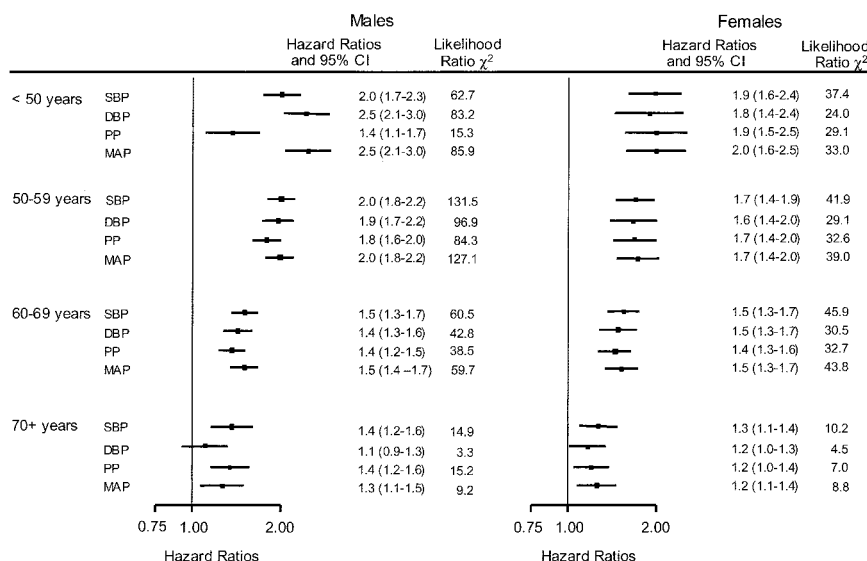


Figure 1. Relation between BP and fatal stroke events by age and gender. Hazard ratios for fatal stroke events, adjusted for cholesterol and smoking, have been calculated for a 1-SD difference in BP for each index. Data are stratified by age (<50, 50 to 59, 60 to 69, and ≥70 years) and gender. Solid squares are larger where there were more events, because their size is proportional to the inverse variance, and horizontal lines represent 95% CIs. Likelihood-ratio χ^2 statistics for fatal stroke events have been calculated by comparing a regression model including a single BP index (and confounders cholesterol and smoking) to the base model (which included cholesterol and smoking but no BP index).

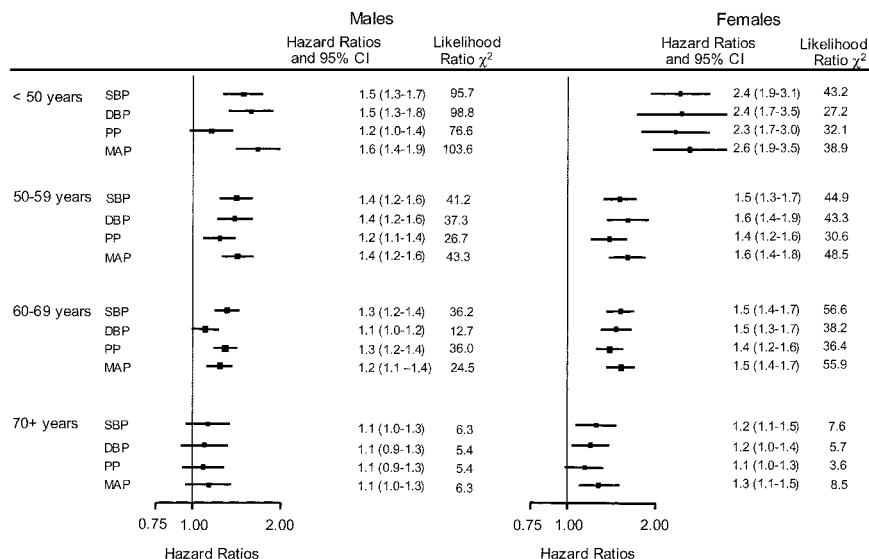


Figure 2. Relation between BP and fatal IHD events by age and gender. Conventions are as described in the legend to Figure 1.

significant for all subgroups (Figure 2). Overall, the hazard ratios were of similar magnitude for DBP, SBP, and MAP but tended to be less for PP. This was consistent when analyses were performed on total events. A comparison of the information provided by each BP index in the regression model by age and gender was undertaken as before (Figure 2). Analyses demonstrated that SBP and MAP were more informative than DBP and PP in most subgroups.

Joint Effects of BP Indices

In secondary analyses, SBP and DBP were simultaneously included in the Cox models to assess whether there was additional information provided for stroke or IHD compared with a model including either SBP or DBP alone. The hazard ratios and SEs for SBP and DBP were similar, regardless of the order in which these indices were included in the model, which is indicative of no major collinearity being present. MAP or PP was not included in models with SBP or DBP, because the former indices are already calculated from the latter.

In most age and gender subgroups, there was a relatively small change in the likelihood-ratio χ^2 statistic for the SBP and DBP model compared with the SBP-alone model ("adding DBP to a model with SBP"). Most of these changes were not significant (Table 2). This indicates that DBP provided no significant incremental contribution over and above the information provided by SBP alone. The results for younger males (<50 years) were less clear. Analyses of total stroke and IHD events produced similar results. In contrast, comparison of the combined SBP and DBP model to the DBP-only model ("adding SBP to a model with DBP") produced significant ($P < 0.05$) changes in the likelihood-ratio χ^2 statistic for most age-gender subgroups. This indicates a significant contribution of SBP over and above that for DBP in these subgroups.

Discussion

These analyses clarify the impact of different BP indices as cardiovascular risk factors in the Asia Pacific region.

Whereas the hazard ratios were of similar magnitude for all indices, the associations were typically stronger for SBP, DBP, and MAP than for PP, particularly in those aged >50 years. Cox models including a single BP index indicated that SBP or MAP provided more information than those including DBP or PP. Analyses also demonstrated broadly similar patterns for males and females, total and fatal events, and stroke and IHD end points. There was, however, attenuation of the association between all BP indices and cardiovascular disease end points with age. In those >50 years of age, the joint effect of SBP and DBP in the Cox model typically resulted in little incremental benefit over and above that of SBP alone. The converse was not true; inclusion of SBP in the Cox model did typically provide additional information over and above that provided by DBP alone.

The finding that overall SBP appears to be statistically more important than DBP in this "Asia Pacific" population is consistent with results from analyses of European and North American populations.^{11-13,16,17} Several analyses have concluded that DBP is superior to SBP in those aged <50 years.^{14,15,18,22} This was not completely borne out in the current study, but the results suggest that SBP and DBP may be of similar importance in the youngest age groups. Many authors have suggested that PP is an important predictor of cardiovascular disease,^{11,12,19,29} possibly more so than other BP measures. However, previous analyses frequently compared the hazard ratio for a 10-mm Hg change in each BP index.^{11,12,19,29} This comparison is dubious, because each index has a different scale; therefore, a 10 mm Hg change in one index is not comparable to a 10 mm Hg change in another. The current analyses standardized the comparison of hazard ratios by using a 1-SD difference in BP, which equated to ≈ 22 mm Hg SBP and 12 mm Hg DBP. In addition, several of the earlier analyses only included MAP and PP but did not include a comparison between PP and SBP.^{11,19,29} Our results are consistent with another recent analysis that used a similar methodology, which also concluded that the associations of SBP and MAP to cardiovascular disease were stronger than those of DBP and PP.¹³

TABLE 2. Increases in Goodness of Fit From Adding BP Indices to the Regression Model, by Age, Gender, and Fatal Outcome

Change in Model by Age Group	Males		Females	
	Likelihood Ratio χ^2	<i>P</i>	Likelihood Ratio χ^2	<i>P</i>
Stroke				
<50 years				
Adding DBP to a model with SBP	24.1	<0.001	0.01	0.9
Adding SBP to a model with DBP	3.6	0.06	13.4	<0.001
50–59 years				
Adding DBP to a model with SBP	2.3	0.1	0.1	0.8
Adding SBP to a model with DBP	36.9	<0.001	12.9	<0.001
60–69 years				
Adding DBP to a model with SBP	2.2	0.1	0.8	0.4
Adding SBP to a model with DBP	19.9	<0.001	16.2	<0.001
70+ years				
Adding DBP to a model with SBP	1.1	0.3	0.1	0.8
Adding SBP to a model with DBP	12.7	<0.001	5.8	0.01
Ischemic heart disease				
<50 years				
Adding DBP to a model with SBP	7.8	0.005	0.03	0.9
Adding SBP to a model with DBP	4.8	0.03	16.1	<0.001
50–59 years				
Adding DBP to a model with SBP	2.6	0.1	3.6	0.06
Adding SBP to a model with DBP	6.5	0.01	5.2	0.02
60–69 years				
Adding DBP to a model with SBP	2.1	0.2	2.1	0.2
Adding SBP to a model with DBP	25.6	<0.001	20.5	<0.001
70+ years				
Adding DBP to a model with SBP	0.1	0.7	1.1	0.3
Adding SBP to a model with DBP	1.0	0.3	3.0	0.08

This table shows increases in goodness of fit from adding DBP to a model including SBP (and also age, gender, cholesterol, and smoking) and vice versa. The greater the likelihood ratio χ^2 , the greater the increase in goodness of fit or “informativeness” with the additional blood pressure index. The *P* value tests the statistical significance of the change.

Although we demonstrated that in most subgroups there was little incremental benefit of including both SBP and DBP in Cox regression models, recent analyses of Multiple Risk Factor Intervention Trial (MRFIT) data suggested that cardiovascular disease risk assessment was improved by considering both SBP and DBP, not just SBP or DBP alone.¹⁵ However, the current analyses were still broadly compatible, because the MRFIT sample only included men aged 35 to 57 years at baseline, and our analyses demonstrated improved goodness of fit with both indices in some younger subgroups.

There are some data limitations that could have influenced the current results, such as the limited number of events in some of the age-gender subgroups. However, even in the age group aged <50 years, there were 128 fatal IHD events (of 269 events) and 88 fatal strokes (of 227 events). The inclusion of a wider sample of studies from APCSC could have limited the comparability of the age-gender subgroups, because different cohort studies would have contributed to different subgroups. Analyses were performed with and

without adjustment for cholesterol and smoking. However, because of the different ways that the cohorts had recorded smoking status, this had to be reduced to a dichotomous variable in these analyses. Data were not available from all cohort studies on diabetic status, electrocardiographic changes, and history of treatment for hypertension. When the current analyses were limited to participants without a history of cardiovascular disease (for those cohort studies that had provided this information), consistent results were obtained. In addition, adjustment for the included risk factors had negligible impact on hazard ratios, and there is no reason to believe that information on additional risk factors would have substantially changed the results.

These analyses were conducted on a large sample with >1800 stroke and 1600 IHD events, more than many previous analyses. Unlike several previous analyses, there was also a high proportion of females. The current analyses were performed on 1-off measures of BP that were not corrected for regression dilution bias,²⁴ but which are more commonly

available than "usual" BP. Correction for regression dilution would have led to stronger associations between all BP indices and end points but would not have changed the relative comparisons of SBP and DBP.²¹ Estimates of the size of the association between BP and cardiovascular disease from all 37 studies included in APCSC have been published elsewhere.²¹ In the age groups <60, 60 to 69, and ≥70 years, a 10-mm Hg lower usual SBP was associated with 54% (95% CI, 53% to 56%), 36% (34% to 38%), and 25% (22% to 28%) lower total stroke risk and 46% (43% to 49%), 24% (21% to 28%), and 16% (13% to 20%) lower total IHD risk, respectively.

Overall, these analyses have demonstrated that SBP and MAP were statistically the most important BP indices, but DBP is still a clinically important measurement and should not be discarded. In a clinical setting, use of SBP will be more practical and relevant than MAP, because the former is easier to measure and interpret.

Perspectives

In summary, this study suggests that although the hazard ratios for all 4 BP indices are similar, SBP is statistically more important than DBP as a risk factor for cardiovascular disease end points in Asia Pacific populations. The patterns were less clear for the youngest age groups; however, less of the burden of cardiovascular disease occurs in these age groups. This may, in part, reflect the fact that prevalent disease and arteriosclerosis selectively reduce DBP.^{30,31} Excessive emphasis on PP should be avoided, because there is no evidence that it has a stronger association with disease than SBP. In contrast, MAP often appeared as important as SBP. However, MAP is likely to have less clinical application than SBP and may be less advantageous overall. SBP is relatively simple to measure owing to a more distinct auscultatory end point than DBP, and MAP requires measurement of both SBP and DBP and a calculation. The use and interpretation of MAP is also unlikely to be practical, because few guidelines exist for this index. Because there is no definite evidence that MAP or PP was clearly superior to DBP and SBP, the 2 former measures do not need to be incorporated into future guidelines.³² Most clinicians think in terms of SBP and DBP, and these 2 measures remain important and clinically useful. However, these data suggest that if time or resources are highly constrained, such as in much-needed epidemiologic surveys in developing countries, very little is lost from measuring only SBP.

Appendix: Asia Pacific Cohort Studies Collaboration

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