Blood pressure levels and risk of cardiovascular disease mortality among Japanese men and women

Blood pressure levels and risk of cardiovascular disease mortality among Japanese men and women: the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study)

Running head: Blood pressure and CVD mortality

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Conflict of interest

The authors declared no conflict of interest. Shinobu Sawachi is presently employed by Sanofi K.K.

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ABSTRACT (248/250 words)

Objective. To examine the association of blood pressure with cardiovascular mortality in real-world settings and investigate whether that association varied by use of antihypertensive medication at baseline.

Methods. Data from 27,728 Japanese men and women, aged 40-79 years, free of stroke, coronary heart disease, cancer, and kidney disease at entry (1988-1990) were used in this study. Mortality surveillance was completed through 2009, resulting 449,800 person-year follow-up. Hazard ratios for cardiovascular mortality were analysed by blood pressure category (based on 2018 European guidelines) at admission.

Results. There were 1,477 deaths from cardiovascular diseases. Relative to high-normal blood pressure at admission, the multivariable hazard ratios (95% confidence intervals) of cardiovascular disease were: 0.85(0.69-1.04) for optimal blood pressure; 0.96(0.81-1.15) for normal blood pressure; 1.26(1.09-1.46) for Grade 1 hypertension; and 1.55(1.31-1.84) for Grade 2-3 hypertension. A similar linear association was observed among persons not taking antihypertensive medication at admission. Among patients treated for hypertension, a U-shaped association with cardiovascular disease mortality was observed; hazard ratios =2.31(1.25-4.27), 1.68(1.05-2.69), 1.56(1.10-2.22), and1.63 (1.13-2.36), respectively. Similar patterns were observed for

66   stroke and coronary heart disease, although not always statistically significant.

67   ***Conclusions.*** Blood pressure categories at baseline were linearly and positively

68   associated with cardiovascular disease mortality overall and also among participants not

69   taking antihypertensive medication. A higher risk of mortality from cardiovascular

70   disease was observed among patients already treated for hypertension with optimal and

71   normal blood pressures than those with high-normal blood pressure, suggesting the

72   importance of careful monitoring of blood pressure and comorbidities of such patients.

73

Introduction

It is well known that high blood pressure (BP) increases the risk of cardiovascular

disease (CVD) [1], and that treatment of hypertension reduces that risk [2]. Clinical

trials have shown that treating hypertension to below-normal BP levels is better for the

prevention of coronary heart disease or stroke among patients with high cardiovascular

risk [3]. On the other hand, several prospective cohort studies have shown that among

patients treated for hypertension treatment to low BP levels was associated with

increased risk of coronary heart disease and/or stroke compared with treatment to

moderate BP levels [4-8].

The causal relations need to be determined through randomized controlled

trials, as observational study designs have inevitable drawbacks (eg confounding

factors). As mentioned, some clinical trials have shown the benefit of lowering BP

below 'normal' levels among strictly selected patients [3]. However, in general practice,

patients with hypertension alongside comorbidities such as atherosclerosis, atrial

fibrillation, and heart failure are sometimes unintentionally treated to low BP levels,

which could lead to an elevated risk of CVD. Clinical trials are typically performed

under 'ideal' trial conditions (following strict inclusion/exclusion criteria and a rigid

protocol), and their results may not be generalizable to general practice where patients

might exhibit hypertension together with such comorbidities as mentioned above. In

addition, many trials, such as the Action to Control Cardiovascular Risk in Diabetes

(ACCORD) [9] or the Systolic Blood Pressure Intervention Trial (SPRINT) [10], with

careful monitoring of adverse events, involved patients with diabetes mellitus (DM) or

high cardiovascular risk. However, despite the possibility of confounding, results from

observational studies of the general population may better reflect clinical realities.

Therefore, the objective of the current study is to provide reliable information

on the relationship between baseline BP levels and long-term mortality from CVD in a

large sample and use differential analysis to examine whether the association varied by

antihypertensive medication use. Our intention is not to try to prove or disprove whether

hypertension should be treated aggressively, but rather to shed light on the outcomes of

patients treated for hypertension in a general (Asian) population.

Methods

Study Cohort and Baseline Questionnaire

Data of the Japan Collaborative Cohort Study for Evaluation of Cancer Risk

(JACC Study), a large nationwide community-based prospective study of Japanese

women and men, were used in our analysis. The JACC study was initiated in 1988-1990,

¹¹¹ and involved 110,585 individuals (46,395 men and 64,190 women) aged 40 to 79 years

¹¹² living in 45 communities across Japan, who participated in municipal health screening

¹¹³ examinations and completed self-administered questionnaires about their lifestyles and

¹¹⁴ medical histories of previous CVD and cancer [11]. Prior to completing the

¹¹⁵ questionnaire, the participants or community representatives provided informed consent

¹¹⁶ to be involved in this epidemiological study, based on guidelines of the Council for

¹¹⁷ International Organizations of Medical Science [12]. The JACC Study protocol was

¹¹⁸ approved by the institutional review boards of Hokkaido University, Osaka University,

¹¹⁹ and the University of Tsukuba.

¹²⁰ Data on blood pressure were available for 29,928 individuals (10,884 men and

¹²¹ 19,044 women) from 30 communities who participated in health examinations

¹²² conducted by municipal governments. After excluding 2,200 individuals from the

¹²³ analysis because of previous history of stroke, coronary heart disease, cancer, or kidney

¹²⁴ disease at the time of baseline inquiry, 27,728 individuals (10,091 men and 17,637

¹²⁵ women) were included in the study.

¹²⁶ Baseline BP was measured as a part of health screening examinations. As standard,

¹²⁷ BP was measured by trained observers using standard mercury sphygmomanometer on

¹²⁸ the right arm of seated participants after 5 minutes rest. The modified classification of

BP from the 2018 European Society of Hypertension-European Society of Cardiology

guidelines [13] was used for classisification. The optimal BP was defined as systolic

pressure <120 mmHg and diastolic pressure <80 mmHg; normal BP as systolic pressure

<130 mmHg and diastolic pressure <85 mmHg; high-normal BP as systolic pressure

130-139 mmHg or diastolic pressure 85-89 mmHg; Grade 1 hypertension as systolic

pressure 140-159 mmHg or diastolic pressure 90-99 mmHg; Grade 2 hypertension as

systolic pressure 160-179 mmHg or diastolic pressure 100-109 mmHg; and Grade 3

hypertension as systolic pressure ≥180 mmHg or diastolic pressure ≥110 mmHg.

Information on antihypertensive medication use and history of DM diagnosis were

obtained from questionnaires.

Mortality Surveillance

To ascertain deaths among the cohort, a systematic review of death certificates, all of

which were forwarded to the local public health centre in each community was

conducted. It is believed that all cohort deaths were recorded, except for those

participants who died after moving from their original community, in which case the

participants' data were censored. The date of moving from the community was verified

using population-registration documents. Mortality data were sent centrally to the

147 Ministry of Health and Welfare, and the underlying cause of death was coded for

148 National Vital Statistics according to the International Classification of Disease, 10th

149 Revision. The mortality follow-up continued through 2009 (except for 3 communities

150 censored at the end of 1999, 1 community at the end of 2003, and 2 communities at the

151 end of 2008). The median follow-up was 18.5 years.

152

153 ***Statistical Analysis***

154 Person-years of follow-up were calculated from the date of the baseline questionnaire to

155 the date of death, emigration from the community, or the end of 2009 (or 1999, 2003,

156 2008), whichever occurred first. The BP exposure was analysed using the 5 categories

157 of the 2018 European Society of Hypertension-European Society of Cardiology [13].

158 Because of the relatively low percentage of the categories of individuals with Grade 3

159 hypertension, the categories of Grade 2 and Grade 3 hypertension were combined. The

160 category of high-normal BP was used as the reference.

161 Age-adjusted means and proportions of selected cardiovascular risk factors were

162 compared across the categories of BP. Cox proportional hazards model were used to

163 calculate the age-, sex-, and multivariable-adjusted hazard ratios (HR) and 95%

164 confidence intervals (CI), by stratification for area (7 regional classifications commonly

165   used in Japan: Hokkaido, Tohoku, Kanto, Chubu, Kinki, Chugoku, and Kyushu).

166   Adjusting factors included body mass index (kg/m^2, sex-specific quartiles), total

167   cholesterol levels (mmol/L, sex-specific quartiles), history of DM (yes versus no),

168   history of kidney diseases (yes versus no), smoking status (never, ex-smoker, or current

169   smoker of 1-19 and ≥20 cigarettes per day), and alcohol intake category (never,

170   ex-drinker, and current drinker at 1-45 and ≥46g ethanol per day). Cardiovascular

171   mortality as the underlying cause included: stroke (International Classification of

172   Disease, 10th Revision, codes I60 to I69), coronary heart disease (codes I20 to I25) and

173   total CVD (codes I01 to I99). We confirmed that there was no violation of the

174   proportional hazards assumption.

175

Results

The overall prevalence of hypertension (systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg and/or use of antihypertensive medication) in this population was 42.3%. As Table 1 shows, the prevalence of anti-hypertensive medication use, DM, and currently drinking, and the mean values of total cholesterol and body mass index were higher in persons with Grade 2-3 hypertension than those with lower BP.

During the maximum of 21.6 (median 18.5) years of follow-up of 27,728 individuals aged 40 to 79 years, 5,239 participants died and 1,309 participants had relocated. The fatalities included 1,477 deaths from CVD; 682 deaths from stroke and 304 deaths from coronary heart disease.

The Figure shows the crude mortality rate, and Table 2 shows multivariable-adjusted HRs of total CVD mortality according to baseline BP category. The crude cardiovascular mortality rates, in all baseline BP categories, were higher among patients treated for hypertension than those untreated (Figure), implying that treated patients already had higher a risk at baseline. As shown in Table 2, higher BP categories were associated linearly and positively with risk of CVD mortality. Relative to high-normal BP, the multivariable HRs were 0.85 (95% CI: 0.69-1.04) for optimal BP, 0.96 (0.81-1.15) for normal BP, 1.26 (1.09-1.46) for Grade 1 hypertension, and 1.55

194   (1.31-1.84) for Grade 2-3 hypertension. A similar linear association was observed

195   among persons with no baseline antihypertensive medication use. Among those treated

196   for hypertension at baseline, however, a U-shaped association with CVD mortality was

197   observed. The multivariable HRs were: 2.31 (1.25-4.27), 1.68 (1.05-2.69), 1.56

198   (1.10-2.22), and 1.63 (1.13-2.36), respectively. Similar relations, but not always

199   statistically significant, were separately observed for stroke and coronary heart disease

200   (Supplemental Table). These trends were essentially similar when men and women were

201   analysed separately (not shown in tables).

202

Discussion

In this large and long-term prospective cohort study of a Japanese general population aged 40-79 years, we confirmed a linear relation between higher BP category at baseline and risk of total CVD mortality. On the other hand, among participants treated for hypertension, we found a U-shaped relation with a nadir at high-normal BP. That association was similarly observed for mortality from stroke and coronary heart disease. The high mortality among patients with hypertension treated to below normal BP levels is unlikely to be causal, due to the 'real-life' nature of the observational data used in our study. Our findings suggest the importance of careful monitoring of BP and comorbidities of patients already undergoing treatment for hypertension who have low BP levels at initial presentation, which is in line with the European Guidelines for the management of arterial hypertension recommendations which state: "Importantly, the impact of BP-lowering on the well being of the patient should be closely monitored, because the increased risk of adverse events (e.g. injurious falls) with lower BP values could be more pronounced in older patients in the real-life setting than in the closely monitored conditions of randomized controlled trials".[13]

A recent study pooling 2 randomized controlled trials (SPRINT and ACCORD) demonstrated that intensive treatment targeting <120 mmHg systolic BP significantly

221 lowered risk of CVD mortality (HR = 0.83 [0.74-0.92]) compared to standard treatment

222 targeting <140 mmHg [3]. A network meta-analysis of 42 trials including 144,220

223 patients found the lowest incidence and mortality from CVD in the 120 to 124 mmHg

224 systolic BP category compared with the higher categories, although they did not

225 examine the risk below 120 mmHg [14]. Our results do not conflict with the results of

226 these trials. The purpose of the clinical trials was to prove the benefit of BP-lowering

227 treatment among high-risk patients under ideal clinical trial conditions. For example,

228 participants in SPRINT were required to have an increased risk of CVD, such as clinical

229 or subclinical CVD (except for stroke), chronic kidney disease, high Framingham risk

230 score, or age of 75 years or older [10]. In that trial, patients who had DM or a history of

231 stroke were excluded. Participants in ACCORD all had DM, and one of the following:

232 CVD, anatomical evidence of atherosclerosis, albuminuria, left ventricular hypertrophy,

233 or at least 2 conventional cardiovascular risk factors (dyslipidemia, hypertension,

234 smoking, or obesity) [9]. The purpose of these trials was to explore the effect of

235 intensive BP lowering in high-risk patients. On the other hand, observational studies, by

236 their nature, cannot prove causality or address the optimal level to reduce high BP, but

237 may more accurately reflect the clinical reality. Patients treated for hypertension to low

238 BP levels may have had a higher prevalence of end-organ defects such as carotid

239 atherosclerosis, cardiac hypertrophy, or chronic kidney disease and, thus, carried a

240 higher risk of CVD. Physicians were likely to aggressively treat hypertension in those

241 patients. However at the baseline of this study (1988-1990), under the criteria of

242 hypertension of ≥160/95 mmHg, the aggressive treatment of hypertension was less

243 common in general practice than it is nowadays. Rather, in general practice,

244 hypertension is typically treated by physicians who are not necessarily experts of

245 cardiology. Patients treated for hypertension may have comorbidities that are likely

246 cause low BP such as atherosclerosis, atrial fibrillation, or heart failure. These patients

247 are sometimes unintentionally treated to below normal BP levels, in which the risk of

248 mortality from CVD increases.

249 As stated, observational data and clinical trial data both have their advantages and

250 disadvantages. Our observational data perhaps more accurately reflect the natural course

251 of a general community-dwelling population, whereas clinical trial data involves a more

252 selected sample of patients who met certain inclusion/exclusion criteria. Accordingly,

253 observational data cannot prove the causality while the trial data have restrictions in

254 terms of generalizability. The U-shape associations among patients already treated for

255 hypertension in the present study do not disprove the beneficial effect of

256 anti-hypertensive medication, but do shed light on the long-term outcomes of patients

257 with hypertension who were under treatment at baseline.

258   Further limitations of the present study should be noted. First, the information on

259 BP and antihypertensive medication use was obtained at baseline only, and thus changes

260 in BP and continued medication use were not taken into account. The nature of the

261 observational study does not allow for controlling variables that may influence

262 behaviour. Second, while we had information on current antihypertensive medication

263 use at baseline, we had no information on the type, dosage, and duration of the drugs

264 prescribed at and after baseline and on hospitalization. In the 1990s, calcium channel

265 blockers were the first-choice antihypertensive drugs in Japan. A previous study showed

266 that survivors of coronary heart disease who took calcium channel blockers had an

267 excess risk of total mortality, with plausible explanations including the established

268 proischemic effect, negative inotropic effects, marked hypotensive effect, and

269 prohemorrhagic effects of these drugs [15]. Assuming these effects may be broadly

270 general, they may in part explain our finding of excess risk of CVD mortality associated

271 with the aggressive treatment of hypertension. Third, we do not have patient data on

272 hypertension-associated end organ damage such as might be provided by

273 electrocardiograms, echocardiograms, or ultrasound imaging of the carotid arteries,

which may mediate the risk of CVD mortality. Fourth, the number of cardiovascular

deaths was small—especially among patients treated for hypertension—although the

present study was large for an Asian cohort study of BP-CVD associations stratified by

treatment. Lastly, the results are based on mortality from CVD rather than its incidence,

which could possibly result in reduced accuracy of diagnosis. In Japan, specification of

underlying causes of death is reported to be reasonable accurate [16,17], although

inaccurate in some instances (eg out of hospital sudden deaths of unspecified origin).

Such misclassification of cardiovascular deaths could differ by BP category, meaning

that our results would be biased.

In conclusion, our results suggest that higher BP categories are linearly and

positively associated with risk of CVD mortality among patients not treated with

antihypertensive medication. However, among treated individuals with optimal and

normal BP levels, we found an excess risk of mortality from total stroke and total CVD

compared with treated individuals with high-normal BP. The present observation

highlights the importance of careful monitoring of the BP and comorbidities of patients

already treated for hypertension who exhibit lower BP levels.

300

301 **Figure legend**

302 Crude mortality rates from total cardiovascular disease according to blood pressure

303 categories among participants with or without treatment for hypertension.

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TABLE 1 Age- and sex-adjusted baseline characteristics according to blood pressure category.

Blood pressure category	No. of participants	Age	Men (%)	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Antihypertensive medication (%)	Current smoker (%)	Current drinker (%)	Total cholesterol (mmol/L)	Body mass index (kg/m^2)	Diabetes mellitus (%)
Total											
Optimal	5717	53	28	109	67	3	24	37	4.98	21.9	2.5
Normal	5771	55	35	122	74	6	22	40	5.08	22.8	2.5
High normal	5740	57	38	132	79	9	22	40	5.15	23.2	3.0
Grade 1 hypertension	7349	59	40	144	86	18	22	42	5.19	23.8	3.6
Grade 2-3 hypertension	3151	61	43	167	95	31	22	43	5.23	24.3	4.1
No medication use											
Optimal	5316	53	28	109	67	0	24	37	4.97	22.0	2.2
Normal	5178	55	36	122	75	0	22	40	5.07	22.8	2.0
High normal	4968	57	38	132	79	0	22	40	5.14	23.2	2.4
Grade 1 hypertension	5649	58	41	144	86	0	21	42	5.19	23.7	2.8
Grade 2-3 hypertension	2042	60	44	166	95	0	22	43	5.22	24.3	3.1
Antihypertensive medication use											
Optimal	85	61	26	111	68	100	23	39	5.01	23.3	7.9
Normal	265	62	27	123	75	100	19	37	5.19	24.0	6.2
High normal	484	62	36	133	78	100	19	41	5.22	23.9	7.3
Grade 1 hypertension	1345	62	35	146	85	100	21	41	5.22	24.1	6.8
Grade 2-3 hypertension	985	62	41	169	95	100	21	40	5.27	24.2	6.5

Blood pressure category was defined as follows: optimal =systolic blood pressure less than 120 mmHg and diastolic blood pressure less than 80 mmHg; normal =120-129 mmHg and/or 80-84 mmHg; high normal =130-139 mmHg and/or 85-89 mmHg; Grade 1 hypertension =140-159 mmHg and/or 90-99 mmHg; Grade 2-3 hypertension =at least 160mmHg and/or 100

TABLE 2. Multivariable hazard ratios and 95% confidence intervals of cardiovascular disease mortality.

Blood pressure category	Person years (PY)	No. of deaths	Crude death rate (/1000PY)	HR1*	95%CI		HR2*	95%CI	
Total									
Optimal	96,836	148	1.53	0.84	(0.69-1.03) ⎤ 0.90 (0.77-1.06)		0.85	(0.69-1.04) ⎤ 0.91 (0.78-1.07)	
Normal	96,176	214	2.23	0.95	(0.80-1.14) ⎦		0.96	(0.81-1.15) ⎦	
High normal	94,711	274	2.89	1.00			1.00		
Grade 1 hypertension	115,434	533	4.62	1.32	(1.14-1.53)		1.26	(1.09-1.46)	
Grade 2-3 hypertension	46,643	308	6.60	1.67	(1.42-1.97)		1.55	(1.31-1.84)	
No medication use									
Optimal	89,893	118	1.31	0.81	(0.65-1.02) ⎤ 0.86 (0.72-1.02)		0.77	(0.61-0.97) ⎤ 0.83 (0.69-0.99)	
Normal	86,169	163	1.89	0.89	(0.73-1.09) ⎦		0.88	(0.71-1.08) ⎦	
High normal	82,260	212	2.58	1.00			1.00		
Grade 1 hypertension	89,446	337	3.77	1.20	(1.01-1.42)		1.19	(1.00-1.42)	
Grade 2-3 hypertension	30,839	188	6.10	1.62	(1.33-1.98)		1.61	(1.32-1.97)	
Antihypertensive medication use									
Optimal	1,333	14	10.50	2.34	(1.27-4.31) ⎤ 1.84 (1.20-2.81)		2.31	(1.25-4.27) ⎤ 1.83 (1.19-2.81)	
Normal	4,119	33	8.01	1.69	(1.06-2.68) ⎦		1.68	(1.05-2.69) ⎦	
High normal	7,410	40	5.40	1.00			1.00		
Grade 1 hypertension	19,965	159	7.96	1.58	(1.12-2.24)		1.56	(1.10-2.22)	
Grade 2-3 hypertension	13,771	110	7.99	1.63	(1.13-2.35)		1.63	(1.13-2.36)	

* HR1: Stratified by area and adjusted for age and sex; HR2: further adjusted for body mass index, serum total cholesterol levels, history of diabetes, smoking status and alcohol intake.

Blood pressure category was defined as follows: optimal =systolic blood pressure less than 120 mmHg and diastolic blood pressure less than 80 mmHg; normal =120-129 mmHg and/or 80-84 mmHg; high normal =130-139 mmHg and/or 85-89 mmHg; Grade 1 hypertension =140-159 mmHg and/or 90-99 mmHg; Grade 2-3 hypertension =at least 160mmHg and/or 100 mmHg, respectively.

Supplemental table. Multivariable hazard ratios and 95% confidence intervals of mortality from stroke and coronary heart disease.

Blood pressure category	Person years (PY)	Stroke						Coronary heart disease					
		No. of deaths	Crude death rate (/1000PY)	HR1*	95%CI	HR2*	95%CI	No. of deaths	Crude death rate (/1000PY)	HR1*	95%CI	HR2*	95%CI
Total													
Optimal to normal	193,012	171	0.89	1.03	(0.81-1.31)	1.04	(0.82-1.32)	60	0.31	0.61	(0.43-0.86)	0.64	(0.45-0.90)
High normal	94,711	116	1.22	1.00		1.00		67	0.71	1.00		1.00	
Grade 1 hypertension	115,434	253	2.19	1.49	(1.19-1.86)	1.39	(1.11-1.73)	106	0.92	1.06	(0.78-1.44)	1.02	(0.75-1.39)
Grade 2-3 hypertension	46,643	142	3.04	1.81	(1.41-2.31)	1.65	(1.29-2.13)	71	1.52	1.48	(1.06-2.08)	1.39	(0.99-1.96)
No medication use													
Optimal to normal	176,061	133	0.76	0.98	(0.75-1.29)	0.94	(0.72-1.24)	43	0.24	0.53	(0.36-0.80)	0.54	(0.36-0.81)
High normal	82,260	89	1.08	1.00		1.00		52	0.63	1.00		1.00	
Grade 1 hypertension	89,446	155	1.73	1.32	(1.01-1.71)	1.30	(1.00-1.69)	74	0.83	1.05	(0.73-1.50)	1.04	(0.73-1.48)
Grade 2-3 hypertension	30,839	91	2.95	1.83	(1.36-2.46)	1.84	(1.36-2.48)	42	1.36	1.38	(0.91-2.08)	1.32	(0.87-2.00)
Antihypertensive medication use													
Optimal to normal	5,452	22	4.04	1.74	(0.94-3.23)	1.70	(0.91-3.17)	9	1.65	2.30	(0.85-6.22)	2.29	(0.84-6.26)
High normal	7,410	19	2.56	1.00		1.00		7	0.94	1.00		1.00	
Grade 1 hypertension	19,965	82	4.11	1.72	(1.04-2.85)	1.67	(1.01-2.78)	27	1.35	1.43	(0.62-3.29)	1.41	(0.61-3.27)
Grade 2-3 hypertension	13,771	49	3.56	1.60	(0.94-2.73)	1.57	(0.91-2.68)	26	1.89	1.79	(0.77-4.16)	1.79	(0.76-4.19)

* HR1: Stratified by area and adjusted for age and sex; HR2: further adjusted for body mass index, serum total cholesterol levels, history of diabetes, smoking status and alcohol intake.

Blood pressure category was defined as follows: optimal to normal =systolic blood pressure less than 130 mmHg and diastolic blood pressure less than 85 mmHg; high normal =130-139 mmHg and/or 85-89 mmHg; Grade 1 hypertension =140-159 mmHg and/or 90-99 mmHg; Grade 2-3 hypertension =at least 160mmHg and/or 100 mmHg, respectively.