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ORIGINAL ARTICLE

Hypertension, concurrent cardiovascular risk factors and mortality: the Singapore Cardiovascular Cohort Study

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The current hypertension (HTN) guidelines recommend the assessment of other cardiovascular disease (CVD) risk factors in individuals with HTN for further management. Few studies in Asian populations have been published to identify the outcome of individuals with HTN and other CVD risk factors. This study aims to assess the effect of HTN alone, and in combination with other CVD risk factors on all-cause and CVD mortality. Three cross-sectional studies carried out in Singapore (baseline 1982–1995) consisting of 5830 persons were grouped by the absence or presence of HTN and CVD risk factors. They were followed-up (mean 14.1 years) by linkage with the National Death Register. Cox's proportional hazards model was used to obtain adjusted hazard ratios (HRs) for risk of mortality. HTN individuals with either <2 CVD risk factors (adjusted HR 1.4; 95% confidence interval (CI) 1.0–1.8) or ⩾2 CVD risk factors (adjusted HR 2.3; 95% CI 1.9–3.0) were at increased risk of all-cause mortality compared to normotensive individuals. The findings were similar for CVD mortality. HTN individuals who also smoked or had diabetes were at highest risk of all-cause mortality, whereas those with elevated total cholesterol/high-density lipoprotein cholesterol, smoked or diabetes had the highest risk for CVD mortality. These findings show that in HTN individuals it is important to assess the presence of other CVD risk factors and manage accordingly.
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Introduction

Hypertension (HTN) is a major modifiable risk factor for cardiovascular disease (CVD) mortality and accounts for up to 30% of deaths worldwide.[1] Globally, approximately two-thirds of stroke and one-half of coronary heart disease is attributable to non-optimal blood pressure.[2] As a majority of patients with HTN have additional CVD risk factors,[3] the HTN guidelines recommend the identification of additional CVD risk factors to institute intervention to both HTN and the other risk factors.[4–6]

Although population-based prospective studies have assessed the effect of blood pressure on all-cause and CVD mortality in Western[7–15] and Asian populations,[16–21] only some have assessed the effect of HTN in combination with other CVD risk factors on mortality and morbidity outcomes.[8,11,14,21] Of these, only one published study has assessed the effect of HTN in combination with other CVD risk factors on mortality outcomes in an Asian population.[21]

Singapore is an island nation comprising approximately 4 million inhabitants all residing in a completely urbanized environment with equitable health-care coverage. The population is composed of three main ethnic groups: Chinese (76.9%), Malays (14.6%) and Asian Indians (6.4%). The aim of this study was to examine the effect of HTN alone, as well as, with other CVD risk factors on all-cause and CVD mortality in an Asian population residing in Asia.

Materials and methods

Participants

This population-based prospective study (Singapore Cardiovascular Cohort Study) was carried out using data and baseline measurements obtained from three previously conducted cross-sectional surveys. These are the Thyroid Heart Study 1982–1985, 1992 National Health Survey and the National University of Singapore Heart Study (1993–1995). The methodologies

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of these studies have been described in detail elsewhere.[22–24] These studies consist of a random sample of individuals living in Singapore. Informed written consent was obtained from participants of all three studies.

Baseline measurements and variables

All participants were examined in the morning following a 10-h overnight fast. Plasma glucose and serum lipid concentrations (total cholesterol, triglyceride and high-density lipoprotein cholesterol (HDL-C)) were measured in two laboratories. However, both were accredited by the World Health Organization International Quality Assurance programs. Low-density lipoprotein cholesterol was calculated using the Friedewald formula. Measurements were standardized within each of the studies. Staff was also trained and quality control was done throughout each survey. In particular, for blood pressure one of the co-authors (KH) measured the blood pressure of all participants in two of the studies (Thyroid Heart Study and National University of Singapore Heart Study). For the 1992 National Health Survey, trained staff took the blood pressure measurements. At least two readings of blood pressure were taken using a standard mercury sphygmomanometer from participants who had rested adequately before measurement. The mean values of the two readings were calculated. Height (to the nearest millimeter) was recorded for all participants without shoes, and weight (in kilograms) was measured for all participants dressed in light clothing using electronic weighing scales. Smoking history was categorized as current smoker or non- and ex-smoker. Alcohol intake was categorized as drinking less than once a month or greater than or equal to once a month as there were few drinkers in this Asian cohort study. Participants were also asked if they have ever been diagnosed as having coronary artery disease, cerebrovascular accident, diabetes or HTN, and whether medication was prescribed. Ethnicity was self-reported at study entry and was classified into Chinese, Malay, Indian and Others.

Participants with HTN were those who had a systolic blood pressure $\geqslant 140$ mm Hg, diastolic blood pressure $\geqslant 90$ mm Hg or currently being treated for HTN. Participants who did not have HTN were described as being normotensive. HTN participants were also further grouped according to the number of additional CVD risk factors that they had. Thus, the groups included (i) normotensive, (ii) hypertensive and <2 CVD risk factors (HTN + <2 CVD risk factors), and (iii) hypertensive and <2 CVD risk factors (HTN + <2 CVD risk factors).

The other CVD risk factors that were assessed include (i) obesity (body mass index $\geqslant 27.5\,kg\,m^{-2}$ using the Asian criteria),[1] (ii) elevated total cholesterol/HDL-C ratio of $\geqslant 5$, (iii) presence of diabetes (previously diagnosed diabetes or current fasting plasma glucose $\geqslant 7.0\,mmol\,l^{-1}$), (iv) personal history of coronary artery disease or cerebrovascular accident (pre-existing CVD) and (v) current cigarette smoking.

Outcomes

Events were obtained by linking individual records (using unique national registry identity card number) to the Singapore Registry of Births and Deaths. The registration of deaths is a compulsory requirement in Singapore and is completed by all registered medical doctors. The data from the registry are considered to be complete and accurate and has been described in detail in a prior publication.[25] It can be considered complete because it is a legal requirement and has to be reported before a burial or cremation is permitted. It is also considered accurate, as the percentage of deaths for ages 30–69 years due to 'symptoms and ill-defined conditions' was low, the value being the following: Chinese 0.4%, Malays 1.5%, Asian Indians 0.2% (for men); and Chinese 0.5%, Malays 1.5% and Asian Indians 0.4% (for women). All outcomes were in coded form using the nineth revision of the *International Classification of Diseases* (ICD-9). All-cause mortality included all deaths that occurred in the cohort until 31 December 2004. The primary cause of death was included. CVD mortality included all deaths due to ischaemic heart disease (ICD-9 410–414) and cerebrovascular accidents (ICD-9 430–438).

Data analysis

Statistical analyses were performed using SPSS (version XIII) (SPSS for Windows, Rel. 13.0.1. 2004. Chicago: SPSS Inc.) and CIA (Confidence Interval Estimation, Version 1.0, copyright 1989: *Gardner Medical Journal* and *British Medical Journal*). Descriptive analyses were done while incidence rates (95% CI) for mortality outcomes were calculated for participants for each of the HTN groups. Cox proportional hazards regression was used to obtain hazard ratios (HR) and 95% confidence intervals (95% CI) for mortality. HR (95% CI) for the HTN group with further adjustment for age, body mass index, total cholesterol/HDL-C ratio as continuous variables, and gender, ethnic group, study (THS, NHS 92, NUH-HS), presence of diabetes, CVD, smoking and alcohol intake as categorical variables. All participants were followed-up till death or censored at 31 December 2004, whichever occurred first. Further subgroup analysis was also done separately for all individuals with HTN ($n=1091$) to determine the effect of having increasing number of CVD risk factors, as well as the effect of individual CVD risk factors.

Interaction terms were created using the HTN/CVD risk factor groups with ethnic group ($P=0.224$ and 0.067), gender ($P=0.285$ and 0.439) and study ($P=0.593$ and 0.970) separately to assess for

significant interaction ($P<0.05$) of these variables in the model for all-cause and CVD mortality, respectively. No significant interaction was found and thus analysis was done with ethnic, gender and study groups combined. Kaplan–Meier curves were also plotted to visually assess the proportional hazards assumption and mortality. These were found to be proportionate over time for the HTN/CVD risk factor groups. An interaction term consisting of follow-up time and the HTN/CVD risk factor groups was also used to test the proportional hazards assumption for occurrence of all-cause and CVD mortality with *P*-values of 0.189 and 0.067 for the interaction terms for each outcome respectively. The *P*-values were not statistically significant (using the cutoff value of $P=0.05$), thus indicating proportional hazard over time.

Results

The study included 5830 participants (81 757 py) with a mean follow-up time of 14.1 years. Participants with HTN were more likely to be male, of Malay and Asian Indian ethnic group and be older than normotensive participants. For other CVD risk factors, participants with HTN were more dyslipidaemic with higher total cholesterol, low-density lipoprotein-cholesterol, triglyceride and total cholesterol/HDL-C ratio, and decreased HDL-C. In addition, these participants also had higher fasting glucose, as well as a higher proportion of obesity, diabetes and a past history of CVD (Table 1). Within the entire cohort 2232 (38.3%), 2073 (35.6%), 1220 (20.9%) and 305 (5.2%) had none, one, two or three or more of these CVD risk factors, respectively. Thus, having two CVD risk factors was used as a cutoff as it allowed for sufficient numbers to be assessed in all the different groups. HTN participants with $\geqslant 2$ CVD risk factors had the highest risk of all-cause (adjusted HR 2.3; 95% CI 1.9–3.0) and CVD (adjusted HR 4.2; 95% CI 2.8–6.2) mortality compared to normotensive participants (Table 2).

Subgroup analysis of only participants with HTN showed a consistent trend of increasing risk for all-cause and CVD mortality for increasing number of CVD risk factors (Table 3). Of these risk factors, the presence of diabetes (HR 1.7; 95% CI 1.3–2.2) and smoking (HR 2.0; 95% CI 1.5–2.8) significantly contributed to all-cause mortality while elevated total cholesterol/HDL-C (HR 2.1; 95% CI 1.2–3.8), diabetes (HR 2.3; 95% CI 1.5–3.5) and smoking (HR 1.9; 95% CI 1.2–3.1) significantly contributed to CVD mortality in HTN participants (Table 4).

Table 1 Gender, ethnic group and CVD risk factor profile for normotensive and hypertensive participants

	Normotensive (n = *4739) (81.3)*	*Hypertensive* (n = *1091) (18.7)*
Gender[a]		
Male	2288 (79.5)	590 (20.5)
Female	2451 (83.0)	501 (17.0)
Ethnic group[a]		
Chinese	2998 (82.7)	626 (17.3)
Malays	929 (78.2)	259 (21.8)
Asian Indians	812 (79.8)	206 (20.2)
Age (years)[b]	35.8 (11.8)	51.9 (11.6)
Total cholesterol ($mmol\,l^{-1}$)[b]	5.4 (1.1)	6.1 (1.3)
LDL cholesterol ($mmol\,l^{-1}$)[b]	3.7 (1.1)	4.2 (1.2)
HDL cholesterol ($mmol\,l^{-1}$)[b]	1.1 (0.4)	1.0 (0.3)
TG ($mmol\,l^{-1}$)[b]	1.0	1.6
Total cholesterol/HDL cholesterol ratio	4.7	5.9
BMI ($kg\,m^{-2}$)[b]	22.6 (3.9)	26.1 (4.4)
Fasting blood glucose ($mmol\,l^{-1}$)[b]	5.4 (1.4)	6.3 (2.3)
Obesity[c]	514 (10.8)	346 (31.7)
Total cholesterol/HDL cholesterol ratio $\geqslant 5$[d]	2085 (44.0)	741 (67.9)
Diabetes mellitus[e]	250 (5.3)	263 (24.1)
Past history CVD[f]	55 (1.2)	78 (7.1)
Current smoker[g]	960 (20.3)	182 (16.7)
Alcohol drinker[h]	434 (9.2)	109 (10.0)

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride.
[a]Numbers (row % for overall, gender and ethnic group, column % for other categorical variables).
[b]Mean (s.d.) for all continuous variables, except for TG and total cholesterol/HDL cholesterol ratio where medians are shown.
[c]Obesity: BMI $\geqslant 27\,kg\,m^{-2}$.
[d]TG/HDL ratio $\geqslant 5$.
[e]Diabetic: includes previously doctor diagnosed diabetes or fasting BSL $> 7\,mmol\,l^{-1}$ (number and column percentages).
[f]Previous CVD: CVD, that is, coronary heart disease or cerebrovascular accident.
[g]Current smoker: smokes at least one cigarette a day (number and column percentages).
[h]Alcohol drinker: drinks more than once a month (number and column percentages).

Table 2 All-cause and CVD mortality for normotensive and hypertensive participants

	Cases (n) *(%)*	*Incidence rate per 1000 py (95% CI)*	*HR (95% CI)*[a]	*HR (95% CI)*[b]
All-cause mortality[c] *(n = 419 deaths)*				
Normotensive	187 (3.9)	2.8 (2.4–3.1)	1.0	1.0
Hypertensive	232 (21.3)	16.9 (14.8–19.1)	6.5 (5.3–7.8)	1.9 (1.5–2.4)
Normotensive	187 (3.9)	2.8 (2.4–3.1)	1.0	1.0
Hypertensive+ < 2 CVD risk factor	79 (14.1)	11.1 (8.6–13.5)	4.3 (3.3–5.6)	1.4 (1.0–1.8)
Hypertensive+ ⩾ 2CVD risk factor	153 (28.8)	23.3 (19.6–26.9)	8.8 (7.1–10.9)	2.3 (1.9–3.0)
CVD mortality[d] *(n = 151 deaths)*				
Normotensive	48 (1.0)	0.7 (0.5–0.9)	1.0	1.0
Hypertensive	103 (9.4)	7.5 (6.1–9.0)	11.2 (7.9–15.7)	3.0 (2.0–4.4)
Normotensive	48 (1.0)	0.7 (0.5–0.9)	1.0	1.0
Hypertensive+ < 2 CVD risk factor	30 (5.4)	4.2 (2.7–5.7)	6.3 (4.0–9.9)	2.1 (1.3–3.4)
Hypertensive+ ⩾ 2 CVD risk factor	73 (13.7)	11.1 (8.6–13.6)	16.3 (11.3–23.4)	4.2 (2.8–6.2)

Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein.
[a]Unadjusted HR (95% CI).
[b]Adjusted HR (95% CI): for the comparison of normotensive and hypertensive groups, HR are adjusted for age, BMI, total cholesterol/HDL cholesterol as continuous variables, and gender, ethnic group, study, presence of diabetes, CVD, smoking and alcohol intake as categorical variables.
[c]All-cause mortality: deaths due to all causes.
[d]CVD mortality: death due to ischaemic heart disease (ICD-9 410–414) and cerebrovascular accidents (ICD-9 430–438).
For the normotensive, hypertensive+ < 2 CVD risk factors, hypertensive+ ⩾ 2 CVD risk factors groups, HR are adjusted for age, gender, ethnic group, study, and alcohol intake.

Table 3 Risk of mortality with increasing number of CVD risk factors in hypertensive participants

Mortality	*Number of CVD risk factors*				P-*value for trend*
	None	*Any one*	*Any two*	*Any three or more*	
All-cause (n = 232 deaths)					
Cases (*n*) (%)	16 (9.1)	63 (16.4)	105 (26.6)	48 (35.3)	
HR (95% CI)[a]	1.0	1.4 (0.8–2.4)	2.0 (1.2–3.4)	2.9 (1.6–5.2)	< 0.001
CVD (n = 103 deaths)					
Cases (*n*) (%)	4 (2.3)	26 (6.8)	48 (12.2)	25 (18.4)	
HR (95% CI)[a]	1.0	2.4 (0.8–6.9)	3.7 (1.3–10.5)	6.0 (2.1–17.5)	< 0.001

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.
[a]HR (95% CI): adjusted for age, study (THS, NHS 92, NUH-HS), ethnicity (Chinese, Malays and Asian Indians), gender and alcohol intake (none or more than once a month, more than or equal to once a month).

Discussion

This study clearly shows that the existence of HTN alone, as well as in combination with other multiple CVD risk factors significantly increases the risk of all-cause and CVD mortality in an Asian population.

Interestingly, the risk of both all-cause and CVD mortality was greater among participants with HTN and more CVD risk factors (adjusted HR 2.3; 95% CI 1.7–3.2 and adjusted HR 4.2; 95% CI 2.8–6.2 for all-cause and CVD mortality, respectively) than in those with less (adjusted HR 1.4; 95% CI 1.0–1.8 and adjusted HR 2.1; 95% CI 1.3–3.4 for all-cause and CVD mortality, respectively). Berglund *et al.*[8] assessed the effects of HTN (systolic blood pressure ⩾160 mm Hg or dystolic blood pressure ⩾ 100 mm Hg or on antihypertensive treatment), hypercholesterolaemia (cholesterol ⩾6.7 mmol l^{-1}) and smoking separately and in combination for all-cause mortality in a cohort of 22 444 Swedish men who were followed-up for an average of 12.2 years. The mortality of individuals with all three risk factors, HTN alone and none of the three risk factors was 21, 13 and 3%, respectively. Another study by Keil *et al.*[11] in 2087, individuals followed over 8 years in Germany found that individuals with HTN (systolic blood pressure ⩾160 mm Hg or systolic blood pressure ⩾95 mm Hg or on antihypertensive treatment), total cholesterol/HDL-C ⩾5.5 and smoking had up to 11 times increased risk of mortality compared to individuals without any of these risk factors, whereas individuals with HTN alone had only approximately three times increased risk of mortality. Our findings in an Asian population are consistent with these findings.

Table 4 Risk of mortality due to other CVD risk factors in hypertensive participants

	All deaths		*CVD deaths*	
	n *(%)*[a]	*HR (95% CI)*[b]	n *(%)*[a]	*HR (95% CI)*[b]
Obesity				
No	163 (21.9)	1.0	78 (10.5)	1.0
Yes	69 (19.9)	1.1 (0.8–1.4)	25 (7.2)	0.8 (0.5–1.2)
Total cholesterol/HDL cholesterol				
Low	50 (14.3)	1.0	14 (4.0)	1.0
High	182 (24.6)	1.1 (0.8–1.5)	89 (12.0)	2.1 (1.2–3.8)
Diabetes				
No	150 (18.1)	1.0	59 (7.1)	1.0
Yes	82 (31.2)	1.7 (1.3–2.2)	44 (16.7)	2.3 (1.5–3.5)
Past history CVD				
No	208 (20.5)	1.0	88 (8.7)	1.0
Yes	24 (30.8)	1.0 (0.7–1.6)	15 (19.2)	1.4 (0.8–2.5)
Current cigarette smoking				
No	163 (17.9)	1.0	72 (7.9)	1.0
Yes	69 (37.9)	2.0 (1.5–2.8)	31 (17.0)	1.9 (1.2–3.1)

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HDL, high-density lipoprotein; HR, hazard ratio.
[a]Numbers and row percentage.
[b]Adjusted HR (95% CI): adjusted for all factors in the tables and also age, study (THS, NHS 92, NUH-HS), ethnicity (Chinese, Malays and Asian Indians), gender and alcohol intake (none or less than once a month, more than or equal to once a month).

Further subgroup analysis in this study showed that participants with HTN who also smoked cigarettes or had diabetes had the highest risk of death from all-causes, while for CVD mortality HTN participants with diabetes, elevated total cholesterol/HDL-C ratio or who smoked cigarettes were at greatest risk. Bearing in mind differences in study design, several studies have also shown similar findings.[26–28] Alderman *et al*.[26] conducted a cohort study upon 6886 treated hypertensive patients with average follow-up of 6.3 years. Participants who were also found to have diabetes at baseline had an increased risk of developing CVD (adjusted HR 2.15; 95% CI 1.58–2.92). In this study, a personal history of CVD (adjusted HR 2.22; 95% CI 1.62–3.05) and being a smoker (adjusted HR 1.52; 95% CI 1.23–1.89) also increased the risk of having a CVD event. Zanchetti *et al*.[27] analysed data from the Hypertension Optimal Treatment (HOT) study of 18 790 hypertensive individuals who were followed for a mean 3.8 years and found that diabetes, smoking and elevated cholesterol were significantly associated with all-cause and CVD morbidity and mortality. A population-based case–cohort study conducted by Glazer *et al*.[28] also showed that the 31% (95% CI 23–39) of incident myocardial infarction among hypertensive individuals could be explained by elevated lipids. Benefit has also been shown in recent clinical trials for individuals who were managed for CVD risk factors other than HTN alone.[29–33] In addition to the effect of dyslipidaemia and diabetes in hypertensive individuals, it is notable that those who smoked were found to have an increased risk of all-cause and CVD mortality. This is of particular concern and calls for interventions for smoking cessation.

Several limitations of this study should be noted. Despite the application of strict control measures, measurement error of variables could have occurred within the studies. Standardization of measurements between studies was also not possible. We have tried to account for this by adjusting for 'study' in the data analysis. Also, although therapeutic advances in the treatment of HTN and other diseases may substantially affect the outcomes of individuals surveyed in different time periods, the assessment of survival using Kaplan–Meier curves and inclusion of an interaction term consisting of follow-up time and HTN/CVD risk factor groups have indicated that the hazards are proportional over time. This indicates that there are still significant and consistent differences in survival for the HTN/CVD risk factor groups despite therapeutic advances. In fact, the effect shown in this study may be an underestimation of the true effect of the risk factors studied. This study also has several strengths. Although derived from three different cross-sectional studies, the participants for the three studies included in this analysis were selected using very similar methodology and represent random samples of the Singapore population.

Thus, an increased risk of mortality was found for HTN participants with concurrent CVD risk factors. This illustrates the importance of identifying and managing all additional CVD risk factors in Asians as recommended by current HTN guidelines.[4–6] Greater attention of medical practitioners towards individuals with HTN in the identification of other concurrent CVD risk factors would certainly be beneficial.

What is known about this topic
- Current western guidelines recommend that individuals with hypertension be assessed for other CVD risk factors and be managed accordingly.[4–6]
- However, few prospective studies in Asian populations have assessed the effect of hypertension in combination with other CVD risk factors on mortality.

What this study adds
- Individuals with hypertension and $\geqslant 2$ CVD risk factors have an increased risk of both all-cause and CVD mortality compared to individuals with hypertension and $\leqslant 2$ CVD risk factors and normotensive individuals.
- In particular, hypertensive individuals who have diabetes or smoke have up to two times increased risk of all-cause and CVD mortality than those without these risk factors.
- It is thus also beneficial for clinicians to screen for and manage additional CVD risk factors in Asian hypertensive patients.

Conflict of interest/disclosure

None. Pfizer had no involvement in the data collection, analysis, interpretation of the data, writing of the paper or decision to submit the paper for publication.

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