

Relationship Between Blood Pressure Values, Depressive Symptoms, and Cardiovascular Outcomes in Patients With Cardiometabolic Disease

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The authors studied the joint effect of blood pressure (BP) and depression on the risk of major adverse cardiovascular outcome in patients with existing cardiometabolic disease. A cohort of 35,537 patients with coronary heart disease, diabetes, or stroke underwent depression screening and BP measurement recorded concurrently. The authors used Cox's proportional hazards to calculate risk of major adverse cardiovascular event (MACE; myocardial infarction/heart failure/stroke or cardiovascular death) over 4 years associated with baseline BP and depression. A total of 11% (3939) had experienced a MACE within 4 years. Patients with very high systolic BP (160–240 mm

Hg; hazard ratio, 1.28) and depression (hazard ratio, 1.22) at baseline had significantly higher adjusted risk. Depression had a significant interaction with systolic BP in risk prediction ($P=.03$). Patients with a combination of high systolic BP and depression at baseline had 83% higher adjusted risk of MACE, as compared with patients with reference systolic BP without depression. Patients with cardiometabolic disease and comorbid depression may benefit from closer monitoring of systolic BP. *J Clin Hypertens (Greenwich)*. 2016;18:1027–1035. © 2016 The Authors. *The Journal of Clinical Hypertension* Published by Wiley Periodicals, Inc.

Blood pressure (BP) reduction is recommended for all patients diagnosed with hypertension by various guideline bodies, especially for patients with cardiometabolic disease (coronary heart disease [CHD], diabetes, and previous stroke), as it is associated with a reduction in the risk of future adverse cardiovascular (CV) outcomes.^{1–4} However, a “J-shaped phenomenon” has also been reported in epidemiological and interventional studies for both systolic BP (SBP) and diastolic BP (DBP), whereby BP lower than 130/80 mm Hg has been associated with higher risk of adverse health outcomes including fatal and nonfatal myocardial infarction (MI) and stroke.^{5–8} The optimal level of BP control in patients with existing cardiometabolic disease remains an area of ongoing debate.^{9,10} Results from the recently published Systolic Blood Pressure Intervention Trial (SPRINT)¹¹ suggest that patients with CHD may have a lower risk of CV events with intensive SBP lowering (<120 mm Hg).¹¹

Patients with existing cardiometabolic diseases such as CHD, diabetes, and stroke are two to three times more likely to experience depressive symptoms than the general population.^{12–14} Moreover, comorbid depression in these patients with cardiometabolic disease is associated with higher risk of subsequent vascular events.^{15–17} Depression screening, as a standalone intervention, in these patient groups has not shown any meaningful benefits in reducing CV events,^{18,19} and it has been recommended that screening should be followed by further evaluation by a professional qualified in the diagnosis and management of depression.²⁰ Depression treatment with models such as collaborative care in cardiometabolic disease patient groups has been found to be beneficial in reducing depressive symptoms and improving treatment adherence but not useful in reducing CV events.^{21,22}

The relationship between depressive symptoms and BP has been investigated in several cross-sectional epidemiological studies.^{23–27} These studies have shown that depression has a nonlinear relationship to SBP and DBP, with greater depressive symptoms at both low and high BP values.^{23–27} One longitudinal study concluded that persistent depression leads to lowering of both systolic and diastolic BP.²⁸

The mediating mechanism for the observed higher risk of CV events in patients with cardiometabolic disease and comorbid depression remains unclear, with factors such as autonomic dysfunction and chronic inflammation proposed as contributors to a causal pathway.²⁹ We

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hypothesized that patients with depression in cardiometabolic disease with poor BP control may represent a “high-risk” subtype, as the above mechanisms have also been associated with poor BP control.^{30,31}

To date, the joint associations of depression and BP with the risk of CV disease has not been studied. In this study, we use data from a large cohort of primary care patients with cardiometabolic disease (CHD/diabetes/stroke), followed up for 4 years, to examine the associations of depression and BP with the risk of subsequent CV events. In doing so, we allow for both nonlinearity of their effects and of interactions between them.

METHODS

Study Design and Setting

The patient sample in this study was recruited from two health boards in the West of Scotland that serve a population of approximately 1.8 million. We received approvals from the National Research Ethics Service and National Services Scotland (NHS) Privacy Advisory Committee and NHS Greater Glasgow and Clyde Enhanced Services data group, which was the authorized “guardian” of this data set. We retrospectively analysed a large routinely collected data set, which was completely anonymous with no patient identifiers, therefore individual patient consent was not obtained.

The local health boards oversaw a program of incentivized depression screening in chronic disease as part of a wider chronic disease management program of Local Enhanced Services (LESs). Family practices in the health boards studied were paid under the LES scheme to carry out a comprehensive annual health assessment, which included depression screening, for all patients with one of the three common cardiometabolic conditions: CHD, diabetes, and stroke. However, there were no penalties for nonadherence. The nurse in the family practice usually carried out the annual health assessment and it lasted for approximately 1 hour. Patients recognized as being “under treatment” for depression at the time of their health assessment were exempt from depression screening. Patients with a positive result on depression screening were offered treatment as per routine care for management of depressive symptoms based on national guidelines.

Participants

The analysis described here was restricted to adults who had a health assessment recorded for at least one of the three conditions between January 4, 2008, to March 31, 2009, and were aged between 18 and 90 years, who underwent depression screening. The “DepChron” data set consisted of a total of 125,143 patients who were in a family practice disease register with a diagnosis of at least one of CHD, diabetes, or stroke in 2008–2009; all of these patients underwent a comprehensive health assessment as part of LES.^{32,33} Patients were labeled as

under treatment for depression and exempt from depression screening if they were noted to be on antidepressants based on their prescription record at the time of depression screening.

Measurement of Clinical Variables

The depression subscale of the Hospital Anxiety and Depression Scale (HADS-D)³⁴ has a range of total score from 0 to 21. A threshold of >7 was used to define the presence of depressive symptoms, as endorsed by national guidelines.³⁵ The area-based Scottish Index of Multiple Deprivations (SIMD) was used as a measure of socioeconomic status, with patients categorized into deciles of deprivation relative to the Scottish population.³⁶ Patients who were identified to have depressive symptoms as a result of depression screening were offered “routine care,” as recommended for management of depressive symptoms in national guidelines.³⁵ A new antidepressant prescription for a period up to 6 months after screening was labeled as “new treatment” for the screened patients. We also analyzed antidepressant prescriptions after excluding amitriptyline as it is often used in the management of chronic pain in primary care. No reliable information was available on the number of patients who were referred for psychological therapies following their depression screening.

SBP and DBP measurements and body mass index (BMI) were recorded determined from height and weight measurements. These BP measurements were performed by the primary care practice nurse during routine clinical assessments. As the data were collected during routine clinical practice, information on methods used for recording the BP (manual or digital; single reading or multiple readings) was not available. A blood sample was collected by the practice nurse at the time of assessment, and the result for total cholesterol was reported in mmol/L and glycated hemoglobin (only available for patients with diabetes) was reported in Diabetes Control and Complications Trial units. We restricted the values for CV risk factors to clinically plausible ranges based on both our clinical judgement and the findings of general population studies. SBP measurements were restricted to a range between 90 mm Hg and 240 mm Hg and DBP to a range between 50 mm Hg and 130 mm Hg.³⁷ Similarly, BMI was restricted to a range between 15 mg/dL and 55 mg/dL,³⁸ total cholesterol between 2 mg/dL and 10 mg/dL,³⁹ and glycated hemoglobin between 3% and 18%.⁴⁰ Observations in the data, which were outside these ranges, were excluded from the analysis.

Measurement of Outcome Variables

We used electronic data linkage methods to measure the outcome variables for the patient cohort recruited in our study for a follow-up duration of 4 years from April 2009 to March 2013. We electronically linked the health records for patients in primary care registers with

the records held by the Information Services Division Scotland for any occurrence of hospitalization or mortality during the follow-up period. We studied four different clinical outcomes for the patients in our study using the *International Classification of Diseases–10th Revision (ICD-10)*.⁴¹ The outcomes studied and their respective ICD-10 codes are as follows:

- 1 Admission due to MI: I21
- 2 Admission due to stroke: I61-I64
- 3 Admission due to heart failure (HF): I50
- 4 Death due to CV causes: I00-I99.

Major adverse CV outcome (CV mortality or admission due to MI/stroke/HF) was used as the composite outcome variable. Patients were censored if they experienced a composite CV outcome as described above or if they died of reasons other than CV causes.

BP Measurement

There is no consensus among various guidelines published internationally for optimal BP targets in patients with existing cardiometabolic disease.^{1–4} We classified BP into five different categories based on clinical judgement to improve interpretability of results. SBP was classified into five categories: very high (160–240 mm Hg), high (140–159 mm Hg), reference (130–139 mm Hg), tightly controlled (120–129 mm Hg), and low (80–119 mm Hg). DBP was also classified into: very high (100–130 mm Hg), high (90–99 mm Hg), reference (85–89 mm Hg), tightly controlled (80–84 mm Hg), and low (40–79 mm Hg). SBP and DBP were also added as continuous variables in the regression models as described below.

Statistical Analysis

We used time-to-event analysis to study the association between three predictors: (1) SBP categories, (2) DBP categories, and (3) presence of depressive symptoms, and the risk of major adverse CV outcome in the study population. Cox's proportional hazards regression analysis was performed, unadjusted and adjusted for potential confounding factors, and the results are presented in terms of hazard ratios (HRs) and 95% confidence intervals (CIs). We performed multivariable analysis adjusting for the following confounders: age (continuous), sex (male and female), socioeconomic status (deprived: SIMD deciles 1–5 vs affluent: SIMD deciles 6–10), initiation of antidepressants (yes/no), number of cardiometabolic comorbidities (range 1–3, representing a combination of one or more of the three cardiometabolic diseases under investigations: CHD, stroke, or diabetes), BMI (normal: 18.5–25 mg/dL, underweight 15–18.5 mg/dL, overweight 25–30 mg/dL, obese 30–50 mg/dL⁴²), and total cholesterol levels (not raised vs raised: >5 mmol/L⁴).

To understand the relationship between BP and depressive symptoms in risk prediction of major adverse CV outcome, if any, we carried out an analysis of variance test to check for interaction between the BP categories and presence of depressive symptoms. In the

event of a significant interaction, we also carried out a subgroup analysis to further study the nature of interaction. In the subgroup analysis, the study sample was divided on the basis of BP categories as described above. In each subgroup, a Cox's proportional hazards regression analysis was performed to study the risk of outcome with the presence of depressive symptoms at baseline, adjusting for potential confounders. Analysis was carried out using the R statistical software, version 3.0.2 (The R Project for Statistical Computing).

Sensitivity Analysis

We performed four different sensitivity analyses in the following patients: those with diabetes, those with affluent socioeconomic class, those with estimated glomerular filtration rate results available at baseline, and those with smoking and alcohol consumption results available.

RESULTS

Patient Population and Clinical Outcomes

A total of 125,143 patients with at least one of the following underwent a comprehensive health assessment in 2008–2009: diabetes (62,275 patients), CHD (62,990 patients), or previous stroke (26,060 patients). A total of 10,670 (8.5%) patients were exempt from depression screening as they were noted to be under treatment for depression and excluded from analysis, while the remaining 114,473 (91.5% of total sample size) were eligible for depression screening. The uptake of depression screening was low and HADS-D was recorded in 35,537 (31.1% of those eligible) of those undergoing the annual health assessment (Figure 1), and it is the data from this subset that we focus on in this paper. A total of 7080 of 35,537 patients had positive HADS-D results (>7) at baseline. Electronic data linkage between primary care disease registers and hospital discharge and mortality records, based on Community Health Index number was successful for 99.4% of patients.

Among the patients who were screened (n=35,537), 12,485 (35.1%) had diabetes only, 11,716 (32.9%) had CHD only, 3558 (10%) had previous stroke only, 7410 (20.8%) had two of these conditions, and 771 (2.1%) had all of the three conditions. Table I compares the demographic features, observed BP values, and the absolute number of adverse CV outcomes for the screened and unscreened population. In the study population of patients with depression screening results (n=35,537), 11% (3939) experienced at least one major adverse cardiovascular event (MACE) within 4 years. In the study population, the observed mean SBP at baseline was 133 mm Hg in the reference SBP group (130–139 mm Hg), 123 mm Hg in the tightly controlled SBP group (120–129 mm Hg), 109 mm Hg in the low SBP group (80–119 mm Hg), 145 mm Hg in the high SBP group (140–159 mm Hg), and 170 mm Hg in the very high SBP group (160–240 mm Hg).

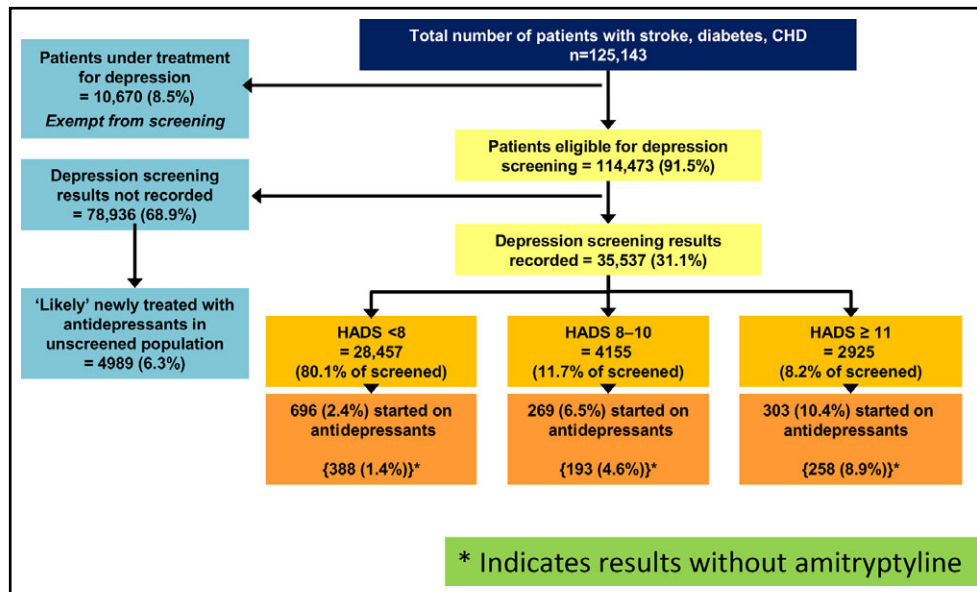


FIGURE 1. Study sample size and recruitment.³³ CHD indicates coronary heart disease; HADS, Hospital Anxiety and Depression Score.

BP, Depressive Symptoms, and Risk of a MACE at 4 Years

In the adjusted multivariable analyses for SBP categories, patients with very high SBP (160–240 mm Hg) and low SBP (80–119 mm Hg) at baseline had a significantly higher risk of a MACE at 4 years compared with patients with reference SBP (130–139 mm Hg) at baseline (Table II). There was no statistical difference in the risk between patients with reference SBP, tightly controlled SBP (120–129 mm Hg), and high SBP (140–159 mm Hg) at baseline. The adjusted risk was 15% higher for patients with low SBP and 28% higher for patients with very high SBP compared with patients with reference SBP at baseline. The presence of depressive symptoms (HADS-D >7) at baseline was associated with a 22% higher adjusted risk of a major CV event compared with those without depressive symptoms (Table II). Figure 2 shows that patients with high SBP had a significantly higher cumulative incidence rate compared with patients in the other SBP categories; similarly, patients with depressive symptoms had a higher cumulative incidence than those without depression.

In the adjusted analysis for DBP categories, none of the DBP categories at baseline had any statistically significant difference in the risk prediction of MACE, compared with the reference (Table II). The results were adjusted for age, sex, socioeconomic status, number of CV comorbidities, BMI, and total cholesterol values at baseline and initiation of antidepressants within 6 months of depression screening. Interestingly, initiation of antidepressants after depression screening did not have any significant impact on the risk of MACE (HR, 0.84; 95% CI, 0.68–1.04; $P=.11$). SBP as a continuous variable was found to have a significant

nonlinear relationship with risk prediction of a MACE while DBP was not a significant predictor as a continuous variable in the multivariable analysis (results not shown). We also repeated the analysis by adjusting for different disease categories and combinations among the three cardiometabolic diseases, and there was no difference in the results (not shown).

Interaction Between SBP and Depressive Symptoms in Risk Prediction of Major CV Event at 4 Years

In the risk prediction of major CV event, the interaction between SBP categories and presence of depressive symptoms was statistically significant ($P=.03$). Patients with low SBP (80–119 mm Hg) only, with very high SBP (160–240 mm Hg) only, and depressive symptoms only at baseline had 10%, 19%, and 17% adjusted higher risks of a major CV event, respectively, compared with those without extremes of SBP and no depressive symptoms (Figure 3). In comparison, patients with both low SBP and depressive symptoms at baseline had a 36% (95% CI, 15%–62%) higher risk while patients with both very high SBP and depressive symptoms had the highest increased risk of 83% (95% CI, 46%–130%) compared with those in the reference SBP group without depressive symptoms.

In the multivariable subgroup analysis of five SBP categories, a nonlinear trend was observed in the association between presence of depressive symptoms and risk prediction of a major CV event at 4 years (Table III). There was no evidence of an association between the presence of depressive symptoms and adjusted risk of major adverse event for the subgroup of patients with reference SBP (130–139 mm Hg) at baseline. Presence of depressive symptoms was associated with significantly higher risk of a major CV adverse

TABLE I. Comparison of the Depression Screened and Unscreened Patient Groups in Existing Cardiometabolic Disease

	Depression Screened (n=35,537)	Depression Unscreened (n=78,936)	P Value
Age, mean (SD), y	69.0 (11.9)	67.0 (14.3)	<.001
White ethnicity, No. (%)	30,693 (92.4)	53,343 (90.3)	<.001
Male sex, No. (%)	20,658 (58.2)	42,727 (54.2)	<.001
Deprived socioeconomic status SIMD deciles ≤ 5 , No. (%)	22,726 (65.3)	51,686 (67.4)	<.001
Number of cardiometabolic conditions, No. (%)			
One	27,356 (77.0)	65,417 (82.9)	<.001
Two	7410 (20.9)	12,265 (15.5)	
Three	771 (2.2)	1254 (1.6)	
Antidepressant initiation, No. (%)	1268 (3.5)	4989 (6.3)	<.001
Systolic blood pressure, No. (%)			
130–139 mm Hg (reference)	8389 (23.6)	13,315 (16.8)	<.001
120–129 mm Hg (tightly controlled)	6864 (19.3)	10,818 (13.7)	
80–119 mm Hg (low)	5711 (16.0)	9258 (11.7)	
140–159 mm Hg (high)	8624 (24.2)	15,969 (20.2)	
160–240 mm Hg (very high)	2514 (7.0)	5778 (7.3)	
Not available	3435 (9.6)	23,802 (30.1)	
Diastolic blood pressure, No. (%)			
85–89 mm Hg (reference)	1909 (5.3)	4219 (5.3)	<.001
80–84 mm Hg (tightly controlled)	7070 (19.8)	13,088 (16.5)	
40–79 mm Hg (low)	20,585 (57.9)	31,724 (40.1)	
90–99 mm Hg (high)	1981 (5.5)	4450 (5.6)	
100–130 mm Hg (very high)	562 (1.5)	1649 (2.0)	
Not available	3430 (9.6)	23,806 (30.1)	
Major adverse cardiovascular outcome (cardiovascular death or admission due to MI/stroke/heart failure), No. (%)	3939 (11)	10,990 (13.9)	<.001

Abbreviations: MI, myocardial infarction; SD, standard deviation; SIMD, Scottish Index of Multiple Deprivation.

event for patients in all other baseline SBP categories. Patients with very high SBP and concurrent depressive symptoms had the highest absolute event rate of 17.7%; moreover, the change in the adjusted risk with addition of depressive symptoms was highest for the subgroup of patients with very high SBP at 55% (Table III).

Sensitivity Analysis

In all four sensitivity analyses, the subgroup of patients with very high SBP and prevalent depressive symptoms were observed to have the highest absolute event rate of CV outcomes. In addition, in SBP subgroup analysis,

TABLE II. SBP, DBP, and Presence of Depressive Symptoms (HADS-D >7) at Baseline and Risk Prediction of Major Adverse Cardiovascular Event (Cardiovascular Death or Admission Due to MI/Stroke/HF) in 35,537 Patients With Previous Stroke, Coronary Heart Disease, or Diabetes at 4 Years of Follow-Up

Predictors at Baseline	Major Adverse Cardiovascular Event	
	Unadjusted HR (95% CI)	Adjusted HR (95% CI) ^a
SBP, mm Hg		
80–119	1.15 (1.04–1.27)	1.15 (1.03–1.29)
120–129	0.99 (0.90–1.09)	1.00 (0.90–1.12)
130–139	1	1
140–159	1.10 (1.00–1.20)	1.07 (0.96–1.18)
160–240	1.43 (1.26–1.61)	1.28 (1.11–1.49)
DBP, mm Hg		
40–79	1.24 (1.07–1.44)	0.94 (0.78–1.12)
80–84	1.05 (0.89–1.23)	0.93 (0.77–1.12)
85–89	1	1
90–99	0.83 (0.67–1.02)	0.90 (0.71–1.14)
100–130	1.03 (0.77–1.39)	1.15 (0.82–1.62)
HADS-D >7	1.23 (1.14–1.32)	1.22 (1.11–1.33)
Reference=HADS-D ≤ 7		

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; HADS-D, Hospital Anxiety and Depression Score-depression subscale; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; SBP, systolic blood pressure.

^aAdjusted for confounders including body mass index, total cholesterol, age, sex, socioeconomic status, number of comorbid conditions, and initiation of antidepressants. Significant results are indicated in bold.

presence of depressive symptoms (against no depressive symptoms) was observed to have the highest adjusted effects size for MACE in the very high SBP subgroup for all four sensitivity analyses. These results are presented in detail in the supplementary information.

DISCUSSION

Summary of Findings

Patients with existing cardiometabolic disease and those with very high and low SBP at baseline were observed to have a significantly higher adjusted risk of a MACE than those with SBP in the reference range. Presence of depressive symptoms at baseline was also associated with a significantly higher risk of a MACE, while DBP was not a significant predictor in the multivariable analysis in either pooled or subgroup analysis. Presence of depressive symptoms compounded the risk of a MACE in patients with very high SBP.

Strengths and Limitations

This study has a number of key strengths, in that the data came from a large, community-based sample reflecting real-life clinical practice, and electronic data

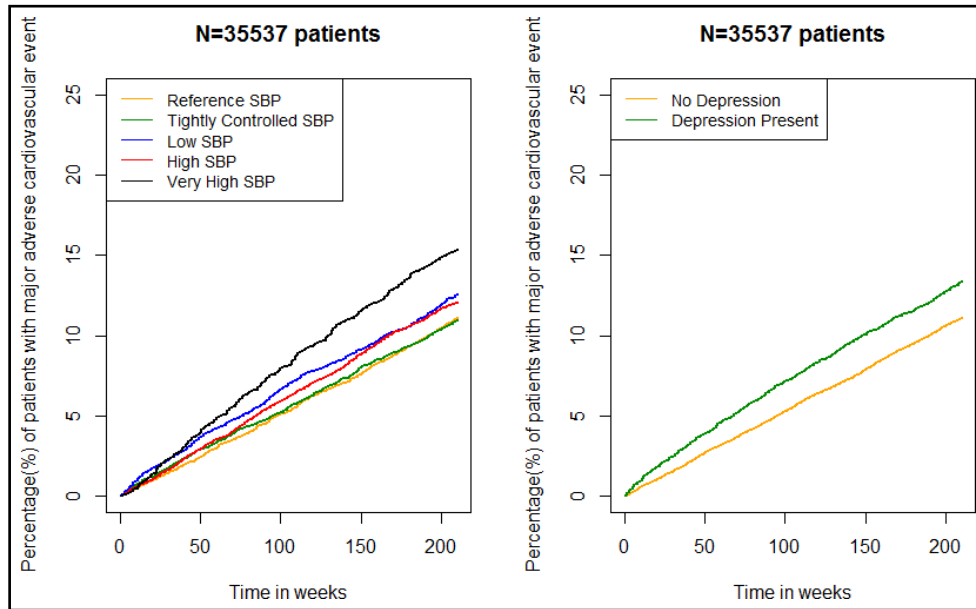


FIGURE 2. Kaplan-Meier plots comparing unadjusted cumulative event rates for major adverse cardiovascular outcome based on systolic blood pressure (SBP) values and presence of depressive symptoms at baseline in patients with existing cardiometabolic disease. A total of 35,537 patients with previous stroke, coronary heart disease, or diabetes. Major adverse cardiovascular event=cardiovascular death or admission due to myocardial infarction/stroke/heart failure. Reference SBP=130–139 mm Hg, tightly controlled SBP=120–129 mm Hg, low SBP=80–119 mm Hg, high SBP=140–159 mm Hg, very high SBP=160–240 mm Hg. Depressive symptoms (defined as Hospital Anxiety and Depression Scale-depression subscale >7) at baseline.

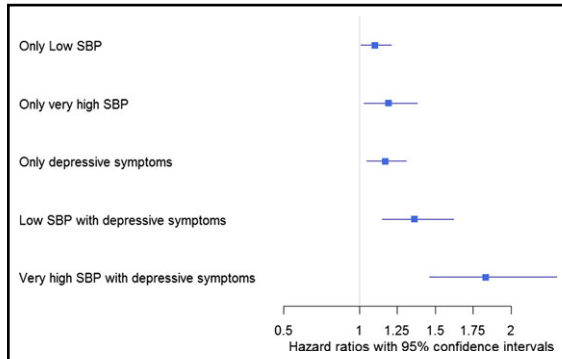


FIGURE 3. Forest plot showing interaction between depressive symptoms and extremes of systolic blood pressure (SBP) at baseline with the risk of major adverse cardiovascular event at 4 years in patients with existing cardiometabolic disease. A total of 35,537 patients with previous stroke, coronary heart disease, or diabetes. A forest plot for comparing cumulative hazard for major adverse cardiovascular event (cardiovascular death or admission due to myocardial infarction/stroke/heart failure) for patients with very high (160–240 mm Hg) and low (80–119 mm Hg) SBP and depressive symptoms (defined as Hospital Anxiety and Depression Scale-depression subscale >7) at baseline.

linkage enabled successful follow-up for the majority of patients in the cohort. There are several limitations. Only a minority of the patients in the sample had depression screening recorded despite incentivization. Consequently, there may be important differences between patients with known depression status and

those whose depression status was unknown that were not recorded in our data. In addition, we did not have information on depression score or CV events for the cohort of patients noted to be “under treatment” for depression at the time of depression screening, which is an important limitation.

The observed association between low SBP at baseline and higher risk of major adverse CV outcomes could be caused by reverse causality, where patients with low SBP could be those with the most severe form of disease. There was no available information on disease severity for the study participants, which is an important limitation. Moreover, we had insufficient information on biobehavioral factors such as smoking status, alcohol consumption, and levels of physical activity and hence we were unable to adjust the main results for these factors. Biobehavioral factors are likely to influence the prevalence of depressive symptoms in cardiometabolic disease patients and, in turn, may affect the ability to make positive health-related behavior changes and influence outcomes.^{43–45} Information on cardiac-related medications was not available for these patients. However, these patients had existing cardiometabolic disease and were attending their primary care providers for annual health assessment. Hence, the majority of them were likely to be taking at least one medication that could lower BP. In addition, we had information only on initiation of antidepressants but did not have information either on duration of antidepressants or on the different class of antidepressants chosen.

TABLE III. Presence of Depressive Symptoms and the Risk of Major Adverse Cardiovascular Events (Cardiovascular Death or Admission for MI/Stroke/HF) for 35,537 Patients With Previous Stroke, Coronary Heart Disease, or Diabetes at 4 Years of Follow-Up Based on SBP at Baseline

	SBP Categories				
	Low, 80–119 mm Hg (n=5711)	Tightly Controlled, 120–129 mm Hg (n=6864)	Reference, 130–139 mm Hg (n=8389)	High, 140–159 mm Hg (n=8624)	Very High, 160–240 mm Hg (n=2514)
Not depressed event rate, No. (%)	492/4376 (11.2)	555/5464 (10.1)	730/6806 (10.7)	776/7028 (11.0)	278/2001 (13.8)
Depressed event rate, No. (%)	192/1335 (14.3)	171/1400 (12.2)	161/1583 (10.1)	226/1596 (14.1)	91/513 (17.7)
Depressed vs not depressed (*adjusted), HR (95% CI)	1.23 (1.01–1.49)	1.34 (1.10–1.63)	0.94 (0.77–1.14)	1.29 (1.08–1.53)	1.55 (1.18–2.03)
P value	<.001	<.001	.54	<.001	<.001

Abbreviations: CI, confidence interval; HADS-D, Hospital Anxiety and Depression Score-depressive subscale; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; SBP, systolic blood pressure.

Adjusted for confounders including body mass index, total cholesterol, age, sex, socioeconomic status, number of comorbid conditions, and initiation of antidepressants. Significant results are indicated in bold.

Moreover, there are other adverse clinical outcomes of significance in this group of patients such as renal failure, angina pectoris, and retinopathy.^{8,46} We did not have information available for these outcomes in our data. Finally, the overall accuracy of depression screening in our study was reliant on HADS-D, which is a self-reported measure and has accuracy-related drawbacks when used for assessing depressive symptoms in patients with cardiometabolic disease in a primary care setting.^{18,47}

Comparison With Existing Literature

The association between presence of depressive symptoms and higher risk of adverse clinical outcomes in patients with preexisting cardiometabolic disease has been previously reported in the literature.^{15–17} SBP at baseline was found to have a nonlinear relationship in our study with the risk prediction of a MACE, which has also been reported in various other studies.^{5,6,8} Our study findings are contrary to the results observed in the SPRINT trial, but there are important differences such as the study design and setting. In addition, the SPRINT trial excluded patients with diabetes and previous stroke, who were included in our study.¹¹ With regards to DBP, our study found that DBP at baseline was not a significant predictor of adverse CV outcomes, and there are studies that have reported similar findings of better predictive power of SBP over DBP in predicting CV outcomes.^{48,49}

This is the first study, to our knowledge, to investigate the interacting relationship between depressive symptoms and BP in risk prediction of adverse clinical outcomes in patients with preexisting cardiometabolic disease.

CLINICAL IMPLICATIONS

Firstly, there may be potential benefits of depression screening for patients with cardiometabolic disease who

have extremes of SBP. Secondly, cardiometabolic disease patients who are diagnosed with comorbid depressive symptoms may benefit from closer monitoring of their SBP for secondary prevention of CV events. Further research is needed in this area before making any clinical recommendations.

CONCLUSIONS

SBP and depressive symptoms at baseline were independent predictors of a MACE at 4 years in patients with existing cardiometabolic disease, while DBP at baseline did not have a significant effect. Presence of depressive symptoms compounded the risk of a MACE in SBP categories both higher and lower than the reference SBP, especially in patients with very high SBP. There may be potential benefits from closer monitoring (over and above routine care) of BP in patients with cardiometabolic disease and comorbid depression. Further research is needed to understand the relationship between extremes of BP and depressive symptoms in patients with existing cardiometabolic disease and the underpinning biological mechanisms.

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Supporting Information

Additional supporting information may be found online in the supporting information tab for this article.

Data S1. Sensitivity Analysis for Patients With Diabetes, Affluent Socio-economic Class, for Patients With Results of Estimated Glomerular Filtration Rate Available and for Patients With Results of Smoking and Alcohol Consumption Available at Baseline

Table S1. Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), and Presence of Depressive Symptoms (HADS-D >7) at Baseline and Risk Prediction of Major Adverse Cardiovascular Event (Cardiovascular Death/Stroke/Myocardial Infarction/New HF

Diagnosis or HF Admission) in a Subset of Patients (n=18,453) With Diabetes at 4 Years of Follow-Up

Table S2. Presence of Depressive Symptoms and the Risk of Major Adverse Cardiovascular Event (Cardiovascular Death/Stroke/Myocardial Infarction/Heart Failure) in a Subset of Patients (n=18,453) With Diabetes at 4 Years of Follow-Up Based on Systolic Blood Pressure at Baseline

Table S3. Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), and Presence of Depressive Symptoms (HADS-D >7) at Baseline and Risk Prediction of Major Adverse Cardiovascular Event (Cardiovascular Death/Stroke/Myocardial Infarction/New HF Diagnosis or HF Admission) in a Subset of Patients (n=12,079) With Affluent Socioeconomic Status at 4 Years of Follow-Up

Table S4. Presence of Depressive Symptoms and the Risk of Major Adverse Cardiovascular Event (Cardiovascular Death/Stroke/Myocardial Infarction/Heart Failure) in a Subset of Patients (n=12,079) With Affluent Socioeconomic Status at 4 Years of Follow-Up Based on Systolic Blood Pressure at Baseline

Table S5. Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), and Presence of Depressive Symptoms (HADS-D >7) at Baseline and Risk Prediction

of Major Adverse Cardiovascular Event (Cardiovascular Death/Stroke/Myocardial Infarction/New HF Diagnosis or HF Admission) in a Subset of Patients With Available eGFR Results (n=15,982) at 4 Years of Follow-Up

Table S6. Presence of Depressive Symptoms and the Risk of Major Adverse Cardiovascular Event (Cardiovascular Death/Stroke/Myocardial Infarction/Heart Failure) in a Subset of Patients With Available eGFR (n=15,982) at 4 Years of Follow-Up Based on Systolic Blood Pressure at Baseline

Table S7. Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), and Presence of Depressive Symptoms (HADS-D >7) at Baseline and Risk Prediction of Major Adverse Cardiovascular Event (Cardiovascular Death/Stroke/Myocardial Infarction/New HF Diagnosis or HF Admission) in Subset of Patients With Smoking and Alcohol Consumption Available (n=13,676) at 4 Years of Follow-Up

Table S8. Presence of Depressive Symptoms and the Risk of Major Adverse Cardiovascular Event (Cardiovascular Death/Stroke/Myocardial Infarction/Heart Failure) in a Subset of Patients With Smoking and Alcohol Consumption Available (n=13,676) at 4 Years of Follow-Up Based on Systolic Blood Pressure at Baseline