

BMJ Open Association between normal systolic blood pressure maintenance and the risk of coronary artery calcification progression in asymptomatic non-diabetic and diabetic adults: a retrospective cohort study using data from the Korea initiatives on coronary artery calcification registry

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To cite: Won K-B, Choi S-Y, Chun EJ, *et al.* Association between normal systolic blood pressure maintenance and the risk of coronary artery calcification progression in asymptomatic non-diabetic and diabetic adults: a retrospective cohort study using data from the Korea initiatives on coronary artery calcification registry. *BMJ Open* 2025;15:e103993. doi:10.1136/bmjopen-2025-103993

► Pre-publication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<https://doi.org/10.1136/bmjopen-2025-103993>).

Received 21 April 2025
Accepted 06 October 2025



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ABSTRACT

Objectives To assess the association of normal systolic blood pressure maintenance (SBP_{maintain}) with coronary artery calcification (CAC) progression in non-diabetic and diabetic subjects at low to intermediate cardiovascular risk.

Design Retrospective cohort study with a mean follow-up of 3.3 years.

Setting Data from the Korea Initiatives on Coronary Artery Calcification registry were analysed.

Participants 10 754 asymptomatic Korean adults (51.5±8.6 years; 84.5% male; 14.2% diabetes) were enrolled. Participants were divided into two groups: normal SBP_{maintain} (<120 mmHg) and ≥elevated SBP_{maintain} (≥120 mmHg) at the time of follow-up CAC scan.

Main outcome measures CAC progression was defined as a difference of ≥2.5 between the square roots ($\sqrt{}$) of the baseline and follow-up coronary artery calcium score (CACS) ($\Delta\sqrt{\text{transformed CACS}}$). Annualised $\Delta\sqrt{\text{transformed CACS}}$ was defined as $\Delta\sqrt{\text{transformed CACS}}$ divided by the interscan period.

Results Compared with non-diabetics, the incidence of CAC progression was higher in diabetics (28.4% vs 47.3%, $p<0.001$) during a mean follow-up of 3.3 years. Normal SBP_{maintain} was inversely associated with an annualised $\Delta\sqrt{\text{transformed CACS}}$ (β : -0.18, 95% CI: -0.25 to -0.12, $p<0.001$) in non-diabetics, but not in diabetics (β : -0.07, 95% CI: -0.31 to 0.19, $p=0.631$). After consecutive adjustments of age, sex, hypertension, dyslipidaemia, obesity, current smoking and baseline CACS, normal SBP_{maintain} showed a lower risk of CAC progression than ≥elevated SBP_{maintain} in non-diabetics; however, this association was not observed in patients with diabetes.

Conclusions Maintaining normal systolic blood pressure was associated with a significantly attenuated CAC

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study assessed the significance of normal systolic blood pressure maintenance (SBP_{maintain}) based on the changes of coronary artery calcification (CAC) in non-diabetic and diabetic adults at low to intermediate cardiovascular risk.
- ⇒ It included adjustment for traditional risk factors and baseline CAC to identify the association of normal SBP_{maintain} with the risk of CAC progression.
- ⇒ The results may not be generalisable to other populations, including due to the specific characteristics of Asian diabetics.
- ⇒ There are recognised limitations related to the retrospective study design.

progression, especially in clinical conditions without established diabetes.

INTRODUCTION

The characteristics of atherosclerosis are obviously different according to the established diabetes.^{1 2} The American College of Cardiology (ACC)/American Heart Association (AHA) has lowered the blood pressure thresholds for diagnosing hypertension.³ The systolic blood pressure intervention trial (SPRINT) reported the significance of intensive systolic blood pressure (SBP) control targeting a normal SBP of <120 mmHg in reducing major adverse clinical events in non-diabetic subjects who are at high risk of cardiovascular (CV) disease.⁴ Recently, the Blood Pressure Control Target in Diabetes

(BPROAD) trial also reported that the incidence of major CV events was lower with intensive treatment targeting a SBP of <120 mmHg than with standard treatment targeting a SBP of <140 mmHg in a diabetic population with pre-specified high CV risk.⁵ These findings confirm that the normal SBP maintenance (SBP_{maintain}) has a benefit for reducing adverse CV events in the population of adults with high CV risk regardless of the presence of established diabetes.

In the asymptomatic adult population, the coronary artery calcium score (CACS) is widely used to stratify the CV risk based on its prognostic value that extends beyond various traditional risk factors.^{6–9} Regarding the prognostic value of coronary artery calcification (CAC) progression, the Heinz Nixdorf Recall (HNR) study has identified that CAC progression makes it difficult to predict the risk of adverse CV events in adults with a high baseline CAC.¹⁰ This finding emphasises the importance of early detection of CAC and its progression for primary prevention of CV disease. However, the benefit of normal SBP_{maintain} for reducing the risk of CAC progression remains uncertain in asymptomatic adults who are at low to intermediate CV risk. Considering (a) the different associations between clinical risk factors and subclinical atherosclerosis according to the presence of diabetes² and (b) the predominant effect of glycaemic control on CAC in established diabetes,¹¹ studying the aforementioned issue is important in both non-diabetic and diabetic subjects. Based on the robust prognostic evidence regarding CACS, numerous studies have suggested the use of CACS to determine therapeutic targets in diverse clinical conditions.^{12–16} A previous study from the Korea Initiatives on Coronary Artery Calcification (KOICA) registry identified that stage 1 hypertension, defined by recent ACC/AHA guidelines at the time of initial CAC scan, was independently associated with CAC progression in asymptomatic adults.¹⁷ However, data on CAC changes related to normal SBP_{maintain} according to the presence of diabetes are scarce. Therefore, the current study aimed to evaluate the association between normal SBP_{maintain} and the risk of CAC progression in an asymptomatic population of Korean adults with and without established diabetes.

METHODS

Study design

In this retrospective cohort study, data from the KOICA registry were analysed.¹⁸ Briefly, a total of 12638 subjects who underwent at least two CAC scan examinations with available data on the status of blood pressure, hypertension and diabetes were enrolled between December 2012 and August 2016. The flow chart of this study is present in the Supplement (online supplemental figure 1). All participants with and without established diabetes were divided into two groups based on the SBP measured at the time of follow-up CAC scan: normal SBP_{maintain} (SBP <120 mmHg) and ≥elevated SBP_{maintain} (SBP ≥120 mmHg).

All data were obtained using a database at the healthcare centre of each site in South Korea (Severance Cardiovascular Hospital; Samsung Medical Centre; Seoul St. Mary's Hospital; Seoul National University Bundang Hospital; Seoul National University Hospital; and Gangnam Heartscan Clinic). Self-reported medical questionnaires were used to collect information on the medical history of the participants. Height and weight were measured with the participants wearing light clothing without shoes. Body mass index (BMI) was calculated as weight (kg)/height (m²). Blood pressure was measured using an automatic manometer on the right arm after resting for at least 5 min; the value of blood pressure after a single measurement was used if blood pressure was in the normal range, whereas the mean value of two measurements was used if it was in the abnormal range. All blood tests, including total cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, glucose and glycated haemoglobin A1C (HbA1C), were conducted after at least 8 hour of fasting. To evaluate CACS, CT was performed using scanners with a ≥16-slice multi-detector (Siemens 16-slice Sensation (Siemens, Forchheim, Germany), Philips Brilliance 40-channel multi-detector CT (Philips Healthcare), Philips Brilliance 256 iCT (Philips Healthcare, Cleveland, OH) and GE 64-slice Lightspeed (GE Healthcare, Milwaukee, WI)). All CAC scans were performed using a scan protocol of standard electrocardiogram-triggering methods. CACS evaluation was performed by experienced CV radiologists at each centre, and the results of CACS measurement were documented in the electronic health records. Informed consent was obtained from all participants.

Traditional CV risk factors were assessed at the time of initial CAC scan. Hypertension was defined as SBP ≥140 mmHg and/or DBP ≥90 mmHg, a previous medical history of hypertension and/or taking anti-hypertensive medication based on the Korean Hypertension Society Guidelines.¹⁹ Diabetes was defined as a fasting glucose level of ≥126 mg/dL, HbA1C of ≥6.5%, a previous diagnosis of diabetes and/or taking anti-diabetic medication.²⁰ Dyslipidaemia was defined as a serum level of total cholesterol of ≥240 mg/dL, HDL cholesterol of ≤40 mg/dL, triglyceride of ≥150 mg/dL, LDL cholesterol of ≥130 mg/dL and/or taking anti-dyslipidaemic medication.²¹ Obesity was defined as a BMI of ≥25.0 kg/m² consistent with the Korean Society for the Study of Obesity Guidelines.²² Current smoking was defined as having smoked at the time of study or within 1 month before study initiation.²¹

CACS was measured using the scoring system previously described by Agatston *et al.*²³ CAC progression was defined using the SQRT method as a difference of ≥2.5 between the square root ($\sqrt{}$) of the baseline and follow-up CACS ($\Delta\sqrt{\text{transformed CACS}}$),^{8 24} considering the large proportion of CACS of 0 (56.5%) in our participants at baseline and the prognostic value of CAC progression defined with SQRT method.⁸ Annualised $\Delta\sqrt{\text{transformed CACS}}$ was defined as $\Delta\sqrt{\text{transformed CACS}}$ divided by

the interscan period. All methods were performed in accordance with the relevant guidelines and regulations. The institutional review board of Severance Cardiovascular Hospital approved the study protocol (IRB No:4-2014-0309). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline for cohort studies.

Statistical analysis

Continuous and categorical variables are presented as mean±SD and as absolute values and percentages, respectively. Continuous variables between two groups were compared using the independent *t*-test or Mann–Whitney U test, as appropriate, while categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate. Univariate linear regression analysis was conducted to assess the association of clinical variables with the annualised $\Delta\sqrt{\text{transformed CACS}}$. Univariate Cox regression analysis was performed to evaluate the association between normal SBP_{maintain} and the risk of CAC progression related to hypertension at baseline. Multiple Cox regression models were employed to assess the risk of CAC progression related to normal SBP_{maintain}; the forced entry method was used to introduce independent variables into the multiple regression models. All statistical analyses were performed using the software IBM SPSS (Statistical Package for Social Sciences, Chicago, Illinois, USA), version 19. Statistical significance was set at *p*<0.05 for all analyses.

Patient and public involvement

None.

RESULTS

Clinical characteristics

The mean age of the participants in this study was 51.5±8.6 years, and 9092 (84.5%) of them were men. Table 1 describes the baseline characteristics of participants according to diabetes. The proportions of normal SBP_{maintain} were 52.4% and 46.4% in non-diabetic and diabetic subjects, respectively. At baseline, the prevalence of CACS 0, 1–100 and >100 was 56.5%, 32.9% and 10.6%, respectively. The proportions of CACS 0, 1–100 and >100 were 60.5%, 30.9% and 8.6% in non-diabetics and 32.4%, 45.2% and 22.4% in diabetics, respectively. Compared with non-diabetics, both the annualised $\Delta\sqrt{\text{transformed CACS}}$ (0.61±1.66 vs. 1.25±2.48) and the incidence of CAC progression (28.4% vs 47.3%) were higher in diabetics during a mean follow-up of 3.3 years (all *p*<0.001) (figure 1). In subjects without established diabetes, both the annualised $\Delta\sqrt{\text{transformed CACS}}$ (0.52±1.71 vs. 0.71±1.59) and the incidence of CAC progression (25.6% vs 31.4%) were lower in normal SBP_{maintain} than in ≥elevated SBP_{maintain} (all *p*<0.001); in contrast, the annualised $\Delta\sqrt{\text{transformed CACS}}$ (1.22±1.95 vs. 1.28±2.86; *p*=0.622) and the incidence of CAC progression (48.9% vs 45.9%; *p*=0.248) were not different between normal

Table 1 Baseline characteristics of participants with and without diabetes

	Non-diabetes (n=9223)	Diabetes (n=1531)	P
Age, years	50.9±8.4	55.3±8.5	<0.001
Male, n (%)	7726 (83.8)	1366 (89.2)	<0.001
SBP, mmHg	119.1±14.9	122.3±15.7	<0.001
DBP, mmHg	74.7±10.6	76.0±10.3	<0.001
BMI, kg/m ²	24.4±2.7	25.2±2.8	<0.001
Obesity, n (%)	3712 (40.3)	775 (50.7)	<0.001
Hypertension, n (%)	2981 (32.3)	878 (57.3)	<0.001
Anti-hypertensive medication, n (%)	2036 (22.1)	667 (43.6)	<0.001
Dyslipidaemia, n (%)	6143 (66.6)	1172 (76.6)	<0.001
Current smoking, n (%)	2536 (28.2)	467 (31.8)	0.005
Laboratory findings			
Total cholesterol, mg/dL	198.7±33.5	189.7±36.2	<0.001
Triglycerides, mg/dL	139.9±87.0	156.6±102.1	<0.001
HDL cholesterol, mg/dL	54.1±16.3	51.3±16.9	<0.001
LDL cholesterol, mg/dL	122.7±31.5	114.7±32.8	<0.001
Glucose, mg/dL	92.9±10.1	128.7±35.4	<0.001
HbA1C, %	5.5±0.4	6.8±1.1	<0.001
Values are given as mean±SD or number (%).			
BMI, body mass index; DBP, diastolic blood pressure; HbA1C, glycated haemoglobin A1C; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.			

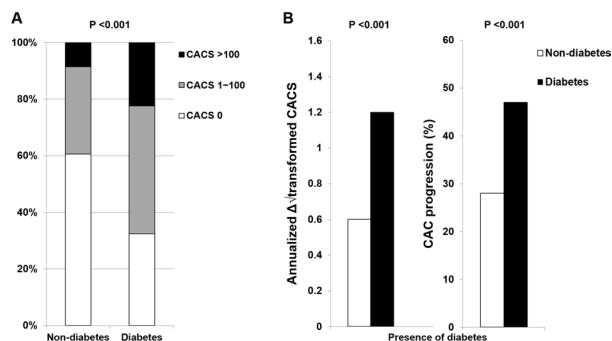


Figure 1 (A) Baseline and (B) changes of CACS according to diabetes. CAC, coronary artery calcification; CACS, coronary artery calcium score.

SBP_{maintain} and $\geq$ elevated SBP_{maintain} in subjects with diabetes (figure 2).

Clinical variables and CAC changes

In participants without diabetes, age, male sex, hypertension, dyslipidaemia, obesity, current smoking and baseline CACS had a positive association with an annualised $\Delta\sqrt{\text{transformed CACS}}$; normal SBP_{maintain} was inversely associated with an annualised $\Delta\sqrt{\text{transformed CACS}}$ (all $p < 0.05$). In participants with diabetes, age, male sex, hypertension and obesity were positively associated with an annualised $\Delta\sqrt{\text{transformed CACS}}$ (all $p < 0.05$); however, unlike in those without diabetes, normal SBP_{maintain} had no significant association with an annualised $\Delta\sqrt{\text{transformed CACS}}$ (table 2).

Normal SBP_{maintain} and risk of CAC progression

Regarding the association between normal SBP_{maintain} and the risk of CAC progression stratified by the presence of hypertension at enrolment (table 3), normal SBP_{maintain} was significantly associated with a decreased risk of CAC progression in non-diabetics regardless of hypertension. In contrast, no significant association was observed between normal SBP_{maintain} and CAC progression in diabetics with and without hypertension at enrolment. In multiple Cox regression models, normal SBP_{maintain} was associated with a decreased risk of CAC progression in non-diabetics after consecutive adjustment of age, sex,

hypertension, dyslipidaemia, obesity, current smoking and baseline CACS; however, this association between normal SBP_{maintain} and the risk of CAC progression was not observed in diabetics (table 4).

DISCUSSION

The CACS is an effective imaging tool for stratifying CV risk over traditional risk factors in the population of asymptomatic adults, with advantages such as low cost, low variability, high reproducibility and easily obtainable images.^{25–28} According to the results of the HNR study,¹⁰ repeated CT scans after 5 years provided the readjustment of CV risk in asymptomatic adults with baseline CACS < 400 . In contrast, additional assessment of CACS did not add prognostic value in subjects with a baseline CACS ≥ 400 , despite its high CV risk. Considering these results emphasising the significance of the early detection of the presence and progression of CAC, the strength of the present study lies in its assessment of the association between normal SBP_{maintain} and changes in CACS in a large cohort of adults without a heavy CAC at baseline; the proportion of participants with a baseline CACS > 400 in our study was only 2.6% (1.9% in non-diabetics and 7.1% in diabetics, respectively).

Based on the evidence regarding (a) different atherosclerotic changes according to the presence of diabetes and (b) the significance of early detection of CAC and its progression, this longitudinal cohort study evaluated the association of normal SBP_{maintain} with the risk of CAC progression in a population of asymptomatic Korean adults with low to intermediate CV risk, stratified by the presence of established diabetes. As is well-known, baseline CACS and incidence of CAC progression were significantly higher in participants with diabetes than in those without diabetes. During a mean follow-up of 3.3 years, normal SBP_{maintain} was independently associated with a decreased risk of CAC progression in non-diabetics, even after adjusting for traditional risk factors and baseline CACS. However, no significant association between normal SBP_{maintain} and the risk of CAC progression was observed in diabetics. These findings suggest that normal SBP_{maintain} may be more effective in preventing CAC progression in asymptomatic adults without established diabetes.

Patients with diabetes have a two- to four-fold higher risk of CV mortality than those without diabetes.²⁹ Diabetes is associated with accelerated atherosclerosis and is considered to be a coronary artery disease (CAD) equivalent.^{30 31} A previous study has reported both higher CAC progression and lower event-free survival in diabetics compared with non-diabetics in proportion to the extent of CAC progression among 596 asymptomatic adults over a mean follow-up of 56 ± 11 months.³² In the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications trials,³³ a baseline CACS > 100 was strongly associated with an increased risk of subsequent occurrence of CV disease and major adverse

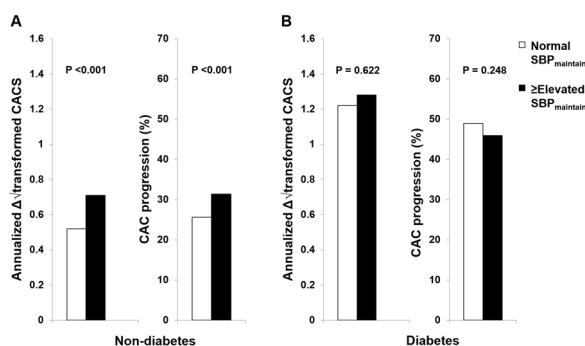


Figure 2 Normal SBP_{maintain} and the changes of CACS in (A) non-diabetics and (B) diabetics. CAC, coronary artery calcification; CACS, coronary artery calcium score; SBP, systolic blood pressure.

Table 2 Association between clinical variables and coronary artery calcification changes according to diabetes status

	Annualised $\Delta\sqrt{\text{transformed CACS}}$					
	Non-diabetes			Diabetes		
	β	95% CI	P	β	95% CI	P
Age, per-1 year	0.04	0.03 to 0.04	<0.001	0.04	0.03 to 0.05	<0.001
Male sex	0.45	0.36 to 0.55	<0.001	0.44	0.03 to 0.84	0.033
Hypertension	0.48	0.41 to 0.55	<0.001	0.29	0.04 to 0.54	0.025
Dyslipidaemia	0.27	0.20 to 0.34	<0.001	0.14	−0.16 to 0.43	0.356
Obesity	0.22	0.15 to 0.29	<0.001	0.27	0.02 to 0.51	0.035
Current smoking	0.10	0.02 to 0.18	0.010	−0.01	−0.28 to 0.27	0.959
Baseline CACS, per-10 unit	0.01	0.01 to 0.02	<0.001	0.00	−0.01 to 0.01	0.262
Normal SBP _{maintain}	−0.18	−0.25 to −0.12	<0.001	−0.07	−0.31 to 0.19	0.631

Univariate linear regression analysis was performed.
CAC, coronary artery calcification; CACS, coronary artery calcium score; SBP_{maintain}, systolic blood pressure maintenance.

events among 1156 adults with type one diabetes over a follow-up of 10 to 13 years. These results have revealed that both baseline and changes in CACS are independent predictors for adverse clinical outcomes in patients with established diabetes.

Approximately 65–85% of diabetics are in the clinical condition of metabolic syndrome.³⁴ A previous large cohort study observed that (a) both diabetes and metabolic syndrome were significantly associated with subclinical atherosclerosis and (b) diabetes strongly influenced subclinical atherosclerosis independent of metabolic syndrome and its individual components.² Data from the KOICA registry previously showed that optimal glycaemic control, defined as HbA1C of less than 7.0% at the time of follow-up CAC scan, attenuated the progression of CAC in asymptomatic patients with diabetes.³⁵ Anand *et al* examined the associations of demographic data, traditional risk factors, glycaemic control, medication use and biomarkers with CAC progression in asymptomatic 398 diabetics who had no history of CAD over a mean follow-up of 2.5±0.4 years.¹¹ In their study, only baseline CACS and suboptimal glycaemic control were determined as independent predictors for CAC

progression among the mentioned clinical variables. Similarly, the present study found that glycaemic control status reflected in HbA1C levels which were measured at the time of follow-up CAC scan was inversely associated with the annualised $\Delta\sqrt{\text{transformed CACS}}$ in participants with diabetes beyond traditional risk factors and baseline CACS (online supplemental table 1). In the subgroup analysis for the pre-specified participants without baseline CAC, SBP (per-1 mmHg increase), which was measured at follow-up CAC scan, was significantly associated with the annualised $\Delta\sqrt{\text{transformed CACS}}$ in non-diabetics, but not in diabetics (online supplemental table 2). Therefore, achieving optimal glycaemic control may be the primary target for preventing CAC progression in asymptomatic diabetics without heavy CAC.

Several studies have reported the usefulness of a lowered blood pressure threshold for diagnosing hypertension according to the 2017 ACC/AHA, even in young adults.^{36 37} In a Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients (STEP) trial,³⁸ intensive SBP control (target of 110–130 mmHg) was associated with a lower incidence of major adverse composite events compared with standard SBP control

Table 3 Association of normal systolic blood pressure maintenance with coronary artery calcification progression according to the comorbidity of hypertension in non-diabetics and diabetics

	CAC progression			P for interaction
	HR	95% CI	P	
Non-diabetes				0.089
No hypertension (n=4392)	0.75	0.67–0.83	<0.001	
Hypertension (n=4831)	0.88	0.78–0.99	0.029	
Diabetes				0.845
No hypertension (n=821)	1.01	0.80–1.26	0.962	
Hypertension (n=710)	1.00	0.82–1.22	0.986	

Univariate cox regression analysis was performed.
CAC, coronary artery calcification.;

Table 4 Risk of coronary artery calcification progression related to normal systolic blood pressure maintenance in non-diabetics and diabetics

	CAC progression		
	HR	95% CI	P
Non-diabetics			
Model 1	0.71	0.66 to 0.77	<0.001
Model 2	0.77	0.71 to 0.83	<0.001
Model 3	0.82	0.75 to 0.88	<0.001
Model 4	0.81	0.75 to 0.88	<0.001
Diabetes			
Model 1	0.93	0.80 to 1.07	0.301
Model 2	1.02	0.88 to 1.19	0.776
Model 3	1.06	0.91 to 1.23	0.477
Model 4	1.08	0.93 to 1.26	0.327

Multivariate Cox regression models with adjustment using forced entry method were analysed.
P values for interaction between diabetes and normal SBP_{maintain} were 0.004.
Model 1: unadjusted.
Model 2: adjusted for age and sex.
Model 3: adjusted for age, sex, hypertension, dyslipidaemia, obesity and current smoking.
Model 4: adjusted for age, sex, hypertension, dyslipidaemia, obesity, current smoking, and baseline CACS.
CAC, coronary artery calcification.;

(target of 130–150 mmHg), in 8511 Chinese patients with hypertension aged 60–80 years. Unlike the SPRINT trial,² 1627 (19.1%) diabetics were included in the STEP trial. According to the results of subgroup analysis in the STEP study, the incidence of composite events was higher in patients with diabetes than in those without diabetes (5.4 vs 3.7%); however, the benefit of intensive SBP control was not significant in diabetics (HR 0.77, 95% CI 0.50 to 1.77). In contrast, recent data from the BPROAD trial confirmed the significance of intensive treatment targeting a SBP of <120 mmHg to reduce the risk of major CV events in a diabetic population with an increased CV risk,⁵ as shown in the SPRINT trial.⁴ Therefore, normal SBP_{maintain} is necessary to achieve a better prognosis in middle- to old-aged adults who are at a high CV risk irrespective of established diabetes. Regarding the prevention of subclinical atherosclerosis in asymptomatic adults with low to intermediate CV risk, normal SBP_{maintain} demonstrated a substantial role in attenuating the risk of CAC progression among non-diabetic participants of the present study. The results of this study might support the recent American Diabetes Association guidelines, which maintain the target systolic and diastolic blood pressure less than 130/80 mmHg for most diabetic patients with hypertension and recommend individualisation of intensive target blood pressure goals based on their CV risk and tolerance to therapy.³⁹

Limitations

This study had some limitations. First, all participants voluntarily visited the hospital for a general health examination, potentially introducing a selection bias. Second, the use of pharmacological agents was not controlled during the follow-up period because of the observational study design. Third, different CT scanners were used across the participating centres; however, all participants were examined with the same CT scanner at both image acquisitions. Fourth, normal SBP_{maintain} was defined based on an SBP of less than 120 mmHg at the time of follow-up CAC scan without considering newly developed hypertension during follow-up periods. Instead, we assessed the association of normal SBP_{maintain} with CAC progression according to the presence of hypertension at enrolment in participants with and without diabetes. Some participants with normal SBP_{maintain} might have been misclassified as having $\geq$ elevated SBP_{maintain} because of the white-coat effect, which could attenuate the effect of $\geq$ elevated SBP_{maintain} on the risk of CAC progression. However, this study identified the significance of normal SBP_{maintain} in non-diabetics for preventing CAC progression, despite the possible effect mentioned above. Fifth, the information on the type of diabetes, the proportion of insulin use and diabetes duration was not obtained in the present study; however, (a) this study did not focus on the effect of anti-diabetic management on CAC progression, (b) most diabetic participants did not have heavy CAC at baseline and (c) the level of HbA1C at follow-up CAC scan was 6.8 $\pm$ 1.1% in diabetics. Possible collider effects should be considered when assessing the risk of CAC progression related to normal SBP_{maintain} among diabetics. Finally, the generalisability of our results may be limited, considering that the characteristics of patients with diabetes in Asia are explicitly different from those of patients with diabetes in other parts of the world.⁴⁰ Nevertheless, to the best of our knowledge, this longitudinal study is the first to assess the association of normal SBP_{maintain} with the risk of CAC progression according to diabetes in a large Asian cohort. Additionally, this study shows the significance of normal SBP_{maintain} in the early stage of coronary atherosclerosis in the absence of established diabetes.

CONCLUSIONS

The current study demonstrates the significance of maintaining normal SBP to prevent CAC progression, particularly in adults without diabetes who are at low to intermediate CV risk, as recently suggested for determining a therapeutic target using CACS in an asymptomatic adult population. Further randomised investigations with larger sample sizes are required to confirm these findings.

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Contributors K-BW and HJC had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: K-BW and HJC. Acquisition, analysis or interpretation of data: K-BW, S-YC, EJC, SHP, JS, HOJ and HJC. Drafting of the manuscript: K-BW. Critical revision of the manuscript for important intellectual content: EJC and HJC. Statistical analysis: K-BW and HJC. Supervision: JS, HOJ and HJC. HJC is responsible for the overall content as the guarantor.

Funding This work was supported by the Institute of Information & Communications Technology Planning & Evaluation (IITP) grant funded by the Korea government (MSIT) (No.2022000972, Development of flexible mobile healthcare software platform using 5G MEC).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The analysis involved de-identification of data from a pre-existing database. The institutional review board (IRB) of Severance Cardiovascular Hospital waived the need for informed consent and approved the use of this de-identified database under IRB protocol number 4-2014-0309.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data may be obtained from a third party and are not publicly available. The data underlying this article cannot be shared publicly because of the lack of permission to share retrospective clinical data outside our institution without authorisation as part of our Institutional Review Board approval. The authors had full access to all data in the study and were responsible for the integrity of the data and the accuracy of the data analysis. The datasets used and analysed in this study are available from the corresponding author upon reasonable request.

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