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Relationship of Hypertension to Coronary Atherosclerosis and Cardiac Events in Patients With Coronary Computed Tomographic Angiography

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Abstract—Hypertension is an atherosclerosis factor and is associated with cardiovascular risk. We investigated the relationship between hypertension and the presence, extent, and severity of coronary atherosclerosis in coronary computed tomographic angiography and cardiac events risk. Of 17 181 patients enrolled in the CONFIRM registry (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) who underwent ≥64-detector row coronary computed tomographic angiography, we identified 14 803 patients without known coronary artery disease. Of these, 1434 hypertensive patients were matched to 1434 patients without hypertension. Major adverse cardiac events risk of hypertension and non-hypertensive patients was evaluated with Cox proportional hazards models. The prognostic associations between hypertension and no-hypertension with increasing degree of coronary stenosis severity (nonobstructive or obstructive ≥50%) and extent of coronary artery disease (segment involvement score of 1–5, >5) was also assessed. Hypertension patients less commonly had no coronary atherosclerosis and more commonly had nonobstructive and 1-, 2-, and 3-vessel disease than the no-hypertension group. During a mean follow-up of 5.2±1.2 years, 180 patients experienced cardiac events, with 104 (2.0%) occurring in the hypertension group and 76 (1.5%) occurring in the no-hypertension group (hazard ratios, 1.4; 95% confidence intervals, 1.0–1.9). Compared with no-hypertension patients without coronary atherosclerosis, hypertension patients with no coronary atherosclerosis and obstructive coronary disease tended to have higher risk of cardiac events. Similar trends were observed with respect to extent of coronary artery disease. Compared with no-hypertension patients, hypertensive patients have increased presence, extent, and severity of coronary atherosclerosis and tend to have an increase in major adverse cardiac events. **(*Hypertension*. 2017;70:00-00. DOI: 10.1161/HYPERTENSIONAHA.117.09402.)**

Key Words: angiography ■ atherosclerosis ■ coronary artery disease ■ hypertension ■ risk factors

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Hypertension affects almost one third of adults, including >7 million patients in the United States[1–3] and is strongly associated with cardiovascular morbidity and mortality.[4–9] Although hypertension is a well-established risk factor for coronary artery disease (CAD),[10] the relationships between hypertension and coronary atherosclerotic plaque stenosis, extent, characteristics, and major adverse cardiac events (MACE) risk have not been examined. Coronary computed tomographic angiography (CTA) has emerged as an accurate noninvasive modality to evaluate coronary atherosclerotic plaque and assess the risk of patients with suspected CAD.[11–14] In this study, we used coronary CTA to investigate the relationship between hypertension and the presence, extent, and severity of CAD and to explore whether hypertension adds to the assessment of atherosclerosis in prediction of MACE.

Methods

Study Population

From 17 181 patients enrolled in the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) registry between 2002 and 2011 who underwent ≥64-detector row coronary CTA at 17 centers, we identified 14 803 patients without known CAD who underwent coronary CTA. Of those, we sequentially excluded patients without information on MACE (n=6889), early revascularization <3 months after coronary CTA (n=1212), and any risk factors used for matching (n=2272), resulting in a population of 4430 patients. Hypertensive and nonhypertensive subjects were matched for age, sex, all other CAD risk factors, including diabetes mellitus, dyslipidemia, current smoking, family history, chest pain symptoms (asymptomatic, atypical, noncardiac, and typical chest pain), and dyspnea using propensity scores.[15] The resulting propensity score was then applied 1:1 to match every hypertensive subject (n=2791) to a corresponding nonhypertensive subject (n=1639) using a Mahalanobis nearest-neighbor matching algorithm with caliper <0.01.[15] After matching, 2868 patients (age 56.4±11.1 years, male 60.8%) comprised the final study population, with 1434 patients with hypertension and 1434 patients without hypertension. The study was followed by Declaration of Helsinki Guidelines, and each institution obtained Institutional Review Board approval. All patients had signed informed consent.

Prescan Risk Factor Assessment

All CAD risk factors were prospectively ascertained before the coronary CTA examination by direct patient interview by a physician or nurse research coordinator and by standardized site surveys. Hypertension was defined as a history of physician-diagnosed high blood pressure or treatment with blood pressure medications. Dyslipidemia was defined as physician-diagnosed dyslipidemia or current treatment with lipid-lowering medications. Diabetes mellitus was defined by physician-diagnosed diabetes mellitus or use of insulin or oral hypoglycemic agents. A smoking history was defined as current smoking or cessation of smoking within 3 months of testing. Family history of CAD was determined by self-report. Chest symptom characteristics (asymptomatic, atypical, noncardiac, and typical chest pain and dyspnea) were recorded.[16]

Imaging Analysis

Coronary CTA was performed using multidetector CT scanners with ≥64 slices detector rows as previously described.[14,17] CT data sets were evaluated for the presence of any plaque and plaque composition (stenosis and extent) on coronary CTA, using a modified 16-segment American Heart Association coronary tree model in accordance with the Society of Cardiovascular Computed Tomographic guidelines.[18] Coronary plaque was identified as hyperdense structure adjacent to lumen of any size or hypodense structure distinct from lumen and per-arterial tissue >1 mm^2 in largest area. Severity of luminal stenosis was classified into 3 groups: none (0% luminal stenosis), nonobstructive (1%–49% luminal stenosis), and obstructive stenosis (≥50% luminal stenosis). For per-vessel analysis, we used a 5-group categorization: no plaque, nonobstructive CAD, and presence of obstructive CAD in 1, 2, or 3 vessels. Left main disease was categorized as a 3-vessel CAD equivalent. For measures of CAD extent and distribution, the segment involvement score (SIS) was defined as the total number of coronary artery segments involved with any plaque.[13] For per-location analysis, we used a 5-group categorization: left main, proximal, mid and distal coronary segments, and side branches, including diagonal branches, obtuse marginal branches, posterior descending artery, and posterior lateral branch. Detected plaques were visually classified as noncalcified plaque (containing no calcification), partially calcified plaque (containing calcification and noncalcified plaque), or calcified plaque (containing only calcification).

Statistical Analysis

Continuous variables were expressed as the mean±SD. The Wilcoxon rank-sum test (for nonparametrically distributed variables) was used to conduct intergroup comparisons between no-hypertension and hypertension groups. Categorical variables were compared using Pearson χ^2 tests.

MACE was defined as all-cause death or nonfatal myocardial infarction. Myocardial infarction was defined by site physicians in accordance with American College of Cardiology/American Heart Association guidelines and the World Health Organization Universal Definition of Myocardial Infarction.[19,20] The log-rank test was used for comparing MACE event rates between the hypertension and no-hypertension groups, and MACE-free survival was further assessed using Cox proportional hazards models and Kaplan–Meier survival curves. We also assessed MACE risk by Cox proportional hazards models in men and women.

In addition, degrees of stenosis severity (normal, nonobstructive, and obstructive CAD ≥50%) and extent of CAD (SIS of 0, 1–5, and >5) were assessed among no-hypertension and hypertension groups in relation to time to MACE by Cox proportional hazards models. Scaled Schoenfeld residuals were used to verify the assumption of proportional hazards of the Cox models.[21] Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated from the Cox models. Area under the curves (AUC) by receiver operator characteristics for prediction of MACE were used to evaluate the added value of hypertension over assessment of coronary atherosclerosis alone (≥50% stenosis or SIS) or the combination of coronary atherosclerosis and clinical factors other than hypertension (other clinical factors [age, sex, diabetes mellitus, dyslipidemia, current smoking, family history, and all chest symptoms]). We also calculated continuous net reclassification index (cNRI)[22] between the models to investigate whether hypertension reclassified patients with respect to MACE risk over the combination of other clinical risk factors and atherosclerosis variables.

All statistical calculations were performed using STATA (Version 11.2; StataCorp LP, College Station, TX) for Windows.

Results

Patient Characteristics

Table 1 demonstrates the baseline characteristics among patients with and without hypertension. Propensity matching resulted in no differences between the groups in age, male sex, other CAD risk factors, and all chest symptoms (P>0.05 for all).

CAD Characteristics on Coronary CTA

Extent and severity of CAD as observed on coronary CTA in patients with and without hypertension are shown in Table 2. About plaque extent and severity stenosis, compared with the no-hypertension patients, hypertension patients manifested a greater SIS and a lower prevalence of absent

Table 1. Clinical Characteristics (n=2868)

Clinical Characteristics	No Hypertension (n=1434)	Hypertension (n=1434)	*P* Value
Age	56.3±11.0	56.6±11.1	0.47
Male sex (%)	60.8	60.8	1.00
Diabetes mellitus (%)	7.5	8.5	0.30
Dyslipidemia (%)	48.0	49.0	0.60
Smoking (%)	16.5	18.3	0.20
Family history (%)	33.3	34.8	0.41
Chest pain status (%)			
Asymptomatic	39.8	37.7	0.17
Noncardiac	14.2	15.8	
Atypical	37.3	35.9	
Typical	8.8	10.7	
Dyspnea	12.8	14.6	0.44

plaque. Hypertension patients possessed greater prevalence of obstructive lesions in 1, 2, or 3 vessels (*P*<0.001). Hypertension patients had more ≥50% stenosis in the proximal and mid coronary arteries and side branches. On plaque characteristics, any noncalcified plaque or calcified plaque was more observed in hypertension patients compared with no-hypertension patients (Table 2).

MACE Risk

One-hundred eighty patients (6.3% of study population) experienced MACE at a mean follow-up of 5.2±1.2 years, occurring in 104 patients of the hypertension group and 76 patients of the no-hypertension group (42 deaths, 34 nonfatal myocardial infarction; 7.3% versus 5.3%, *P*=0.03; Tables 3 and 4). Kaplan–Meier curve demonstrated that MACE were more common in the hypertension versus the no-hypertension subjects (*P*<0.01; Figure 1). By Cox proportional analysis, hypertension subjects experienced higher MACE risk than no-hypertension subjects (HR, 1.4; 95% CI, 1.0–1.9; *P*=0.03). On a subanalysis by sex, in both of men and women, MACE tended to be more common in the hypertension versus the no-hypertension subjects (HR, 1.4; 95% CI, 0.9–2.0; *P*=0.12 for men, and HR, 1.4; 95% CI, 0.9–2.3; *P*=0.14 for women).

Considering the CTA findings, the risk of MACE was progressively higher in the subjects with nonobstructive CAD and those with obstructive CAD when compared with those with no-CAD (Figure 2A). A trend toward a higher odds ratio was observed among hypertension patients with normal coronary arteries; however, it did not reach statistical significance (HR, 1.9; 95% CI, 1.0–3.6; *P*=0.06). In patients with nonobstructive CAD, the HRs of the hypertension and no-hypertension groups were similar. In the obstructive CAD group, the HR in the hypertension group was only slightly higher than that in the no-hypertension group (Figure 2A).

On the extent of CAD, similar findings were observed. The risk of MACE was also progressively higher in the subjects with SIS of 1 to 5 and those with SIS of >5 when compared with those with no-CAD. The HRs of the hypertension group in the SIS of 1 to 5 and SIS of >5 groups were only slightly higher than the no-hypertension group (Figure 2B).

Table 2. CAD Characteristics on Coronary CTA (n=2868)

CAD Characteristics on Coronary CTA	No Hypertension (n=1434)	Hypertension (n=1434)	*P* Value
SIS (median; IQR)	0 (0–2)	1 (0–3)	<0.0001
No. of vessels with plaque and ≥50% stenosis (%)			
No plaque	53.0	43.7	<0.001
Nonobstructive plaque (1%–49%)	33.3	37.7	
1-vessel disease (≥50%)	9.5	12.1	
2-vessel disease (≥50%)	2.6	4.4	
3-vessel disease (≥50%)/ Left main	1.6	2.2	
Distribution for any coronary artery disease (%)			
Left main	12.6	14.1	0.24
Proximal	38.2	46.6	<0.001
Mid	29.3	36.0	<0.001
Distal	14.1	18.6	0.002
Side branches	14.7	18.4	0.01
Distribution for coronary artery disease with ≥50% stenosis (%)			
Left main	0.3	0.6	0.18
Proximal	7.5	10.0	0.02
Mid	8.2	10.3	0.06
Distal	3.4	4.6	0.12
Side branches	4.7	7.0	0.01
Plaque characteristics (%)			
Noncalcified plaque	13.2	17.8	0.001
Partially calcified plaque	19.5	22.2	0.08
Calcified plaque	24.3	28.2	0.02

CAD indicates coronary artery disease; CTA, computed tomographic angiography; IQR, interquartile range; and SIS, segment involvement score.

The incremental added value of hypertension in prediction of MACE over clinical and CTA variables is shown in Table 4. The presence of obstructive CAD was predictive of MACE (model 1; AUC, 0.648). The combination of other clinical factors increased this prediction (model 2; *P*<0.0001 for cNRI and *P*<0.0001 for AUC). When hypertension was then added (model 3), there was a significant increase in cNRI (*P*=0.03), and a trend toward increase in the AUC (*P*=0.055). Similar

Table 3. MACE Risk

MACE Risk			
MACE	No Hypertension (n=1434)	Hypertension (n=1434)	*P* Value
MACE (%, n)	5.3 (76)	7.3 (104)	0.03
Deaths (%, n)	2.9 (42)	3.9 (56)	
Nonfatal MI (%, n)	2.4 (34)	3.4 (48)	

MACE indicates major adverse cardiac events; and MI, myocardial infarction.

Table 4. Predictors of MACE

Predictors of MACE						
Models	cNRI (95% CI)	*P* Value	% Events Reclassified	% Nonevents Reclassified	AUC	AUC *P* Value
Stenosis severity of CAD						
Model 1	…	…	…	…	0.648	
Model 2 (vs model 1)	0.39 (0.24–0.54)	<0.0001	14%, *P*=0.053	24%, *P*<0.0001	0.729	<0.0001
Model 3 (vs model 2)	0.17 (0.02–0.32)	0.03	16%, *P*=0.04	1%, *P*=0.59	0.734	0.055
Extent of CAD						
Model 4	…	…	…	…	0.678	
Model 5 (vs model 4)	0.41 (0.26–0.56)	<0.0001	17%, *P*=0.03	24%, *P*<0.0001	0.721	0.001
Model 6 (vs model 5)	0.17 (0.02–0.32)	0.03	16%, *P*=0.04	1%, *P*=0.59	0.726	0.052

Model 1: Stenosis severity ≥50%. Model 2: Age, sex, and other risk factors+stenosis severity ≥50%. Model 3: Age, sex, and other risk factors+stenosis severity ≥50%+HT. Model 4: SIS. Model 5: Age, sex, and other risk factors+SIS. Model 6: Age, sex, and other risk factors+SIS+HT. Other risk factors are diabetes mellitus, dyslipidemia, smoking, family history, and chest symptoms. AUC indicates area under the curve; CAD, coronary artery disease; CI, confidence interval; cNRI, continuous net reclassification index; HT, hypertension; MACE, major adverse cardiac events; MI, myocardial infarction; and SIS, segment involvement score.

results were observed with respect to the extent of CAD. The SIS alone was predictive MACE (model 4; AUC, 0.678). The combination of other clinical factors increased this prediction (model 5; *P*<0.0001 for cNRI and *P*=0.0001 for AUC). When hypertension was added (model 6), a significant increase in cNRI (*P*=0.03) and an increase in the AUC were observed (*P*=0.052).

Discussion

This study demonstrated that patients with hypertension had more advanced coronary atherosclerosis by coronary CTA and future MACE risk compared with those without hypertension. When stratifying by sex, there was a trend toward increased MACE risk in hypertension in both men and women. Patients with hypertension more frequently had any CAD, with higher prevalence of any CAD and of 1-, 2-, and 3-vessel obstructive CAD in each category, as well as CAD ≥50% stenosis in the proximal, mid, and side branches. Hypertension patients also had greater prevalence of any noncalcified plaque and calcified plaque. When stratifying by the extent and severity of CAD, MACE risk in the hypertension group was slightly higher than that in the non-hypertension group across the CAD categories. There was a trend toward incremental predictive value of hypertension over other risk factors and the extent or severity of CAD.

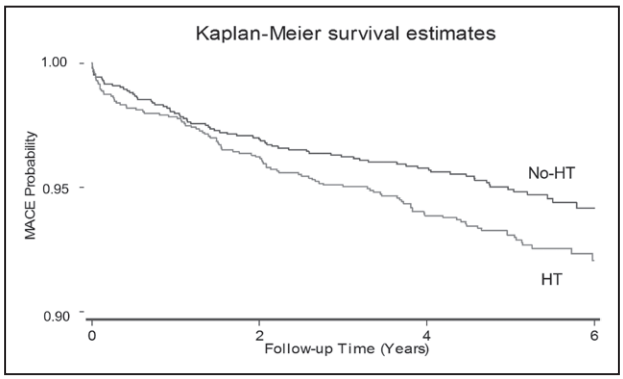

Figure 1. Kaplan–Meier curve for major adverse cardiac events (MACE) in patients with no known coronary artery disease (CAD) among the absence and presence of hypertension (HT).

It is well known that hypertension is a main cardiovascular risk factor and related to worsening prognosis.[4,5,7–9] To our knowledge, however, no previous studies have shown the direct relation of hypertension to CAD characteristics, including the presence, extent, and severity of CAD on coronary CTA and MACE risk that is described in this article.

Using the current registry, our group previously reported the relationship between diabetes mellitus and current smoking and the presence, extent, and severity of coronary atherosclerosis on coronary CTA, as well as the relationship of the coronary CTA findings to future adverse outcomes.[23,24] The findings of this study suggest that the presence of hypertension per se may not add as much incremental prognostic value as these other risk factors after taking into account the presence, extent, and severity of coronary CTA.

Hypertension has been previously shown to be a predictor of the extent of coronary atherosclerosis as assessed by coronary artery calcium.[25] Both diabetes mellitus and smoking were found to be stronger predictors of coronary atherosclerosis than hypertension. Extensive epidemiological data have also demonstrated that hypertension is an independent risk factor for coronary atherosclerosis and for future cardiac events,[26,27] but that it is less strong a predictor than diabetes mellitus and smoking.[25] Our findings are concordant with the previous data with respect to coronary atherosclerosis, including a relationship to increasing amounts of obstructive CAD and with showing a trend toward association with MACE events.

How hypertension results in increase in coronary atherosclerosis has been extensively studied. The principal underlying pathophysiologic mechanism is considered to be a mechanical one related to pulse pressure.[28] Wide pulse pressure has been reported to be associated with increased cardiac events.[29–33] Both increased pulse pressure and systolic pressure contribute to endothelial dysfunction, which facilitates the entry of low-density lipid cholesterol into the blood vessel

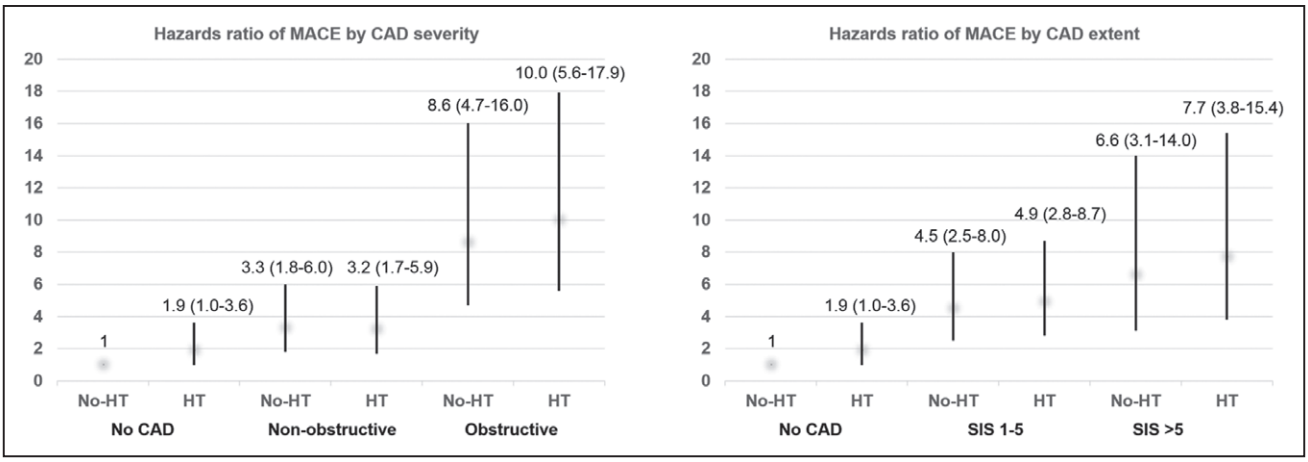

Figure 2. A, **Left**, Cox proportional hazard models by normal, nonobstructive, and obstructive coronary artery disease (CAD) among no-hypertension (no-HT) and hypertension (HT) groups. **B**, **Right**, Cox proportional hazard models by segment involvement score (SIS) 0, 1 to 5, and >5 among no-HT and HT groups.

wall, initiating the atherosclerotic process.[34] Hypertension also is a cause of left ventricular hypertrophy (LVH),[35,36] which has been implicated as a cause of coronary atherosclerosis, myocardial infarction, arrhythmia, cardiac failure, or cardiac death.[34,37–39] LVH is associated with collagen deposition within the left ventricle.[34] This process is considered to explain the frequent association of LVH with midmyocardial scarring on cardiovascular magnetic resonance, which is associated with increase in cardiac events.[40]

Of interest, in this study, in patients with no evidence of CAD on coronary CTA, those with hypertension had a >2-fold MACE risk compared to those with no-hypertension. An increased risk of events in these patients could have been related to LVH; however, information on LVH was not present in the CONFIRM database.

Limitations

There are several limitations in this study. Data on duration and severity of hypertension, as well as information on LVH, did not exist in the current registry. Information was not uniformly available on specific antihypertensive medications at the time of testing. Further, no information was available on the effectiveness of blood pressure control after testing which may have affected MACE risk.[41] We have included various CAD descriptors, including the extent, stenosis severity, basic characteristics, and location of CAD. However, other variables, such as vulnerable plaque features or bifurcation lesions, that might be associated with MACE risk were not available in this study. The number of events by sex was small and may have led to the finding that a trend toward increased MACE divided by sex was not statistically significant.

Perspectives

Compared with patients without hypertension, hypertensive patients have increased presence, extent, and severity of coronary atherosclerosis and tend to have an increase in MACE events. The findings support the concept of lifestyle modification regardless of sex to optimize CAD risk factors, including hypertension, to reduce future cardiovascular events as suggested by current guidelines.[42]

Conclusions

Hypertensive patients had greater amount of coronary atherosclerosis and greater risk of MACE compared with nonhypertensive patients, independent of other clinical risk factors and of the presence of obstructive CAD or extent of CAD. Further, hypertensive individuals with an increasing degree of CAD stenosis severity and extent of CAD experienced modestly increase rates of MACE compared with nonhypertensive patients.

Disclosures

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Novelty and Significance

What Is New?

- This study is the first study showing the relation of hypertension to the presence, extent, and severity of coronary artery disease on coronary computed tomographic angiography and to risk of major adverse cardiac events among patients without known coronary artery disease.

What Is Relevant?

- The presence of hypertension per se may not add as much incremental prognostic value as other risk factors after taking into account the presence, extent, and severity of coronary computed tomographic angiography.

Summary

Patients with hypertension had greater prevalence of extent and stenosis severity of coronary artery disease and modestly increased major adverse cardiac events risk compared with those without hypertension.

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