

Early Onset Hypertension Is Associated With Hypertensive End-Organ Damage Already by MidLife

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Abstract—Early onset hypertension confers increased risk for cardiovascular mortality in the community. Whether early onset hypertension also promotes the development of target end-organ damage (TOD), even by midlife, has remained unknown. We studied 2680 middle-aged CARDIA study (Coronary Artery Risk Development in Young Adults) Study participants (mean age 50±4 years, 57% women) who underwent up to 8 serial blood pressure measurements between 1985 and 2011 (age range at baseline 18–30 years) in addition to assessments of echocardiographic left ventricular hypertrophy, coronary calcification, albuminuria, and diastolic dysfunction in 2010 to 2011. Age of hypertension onset was defined as the age at first of 2 consecutively attended examinations with blood pressure ≥140/90 mm Hg or use of antihypertensive medication. Participants were divided in groups by hypertension onset age (<35 years, 35–44 years, ≥45 years, or no hypertension). While adjusting for TOD risk factors, including systolic blood pressure, we used logistic regression to calculate odds ratios for cases (participants with TOD) versus controls (participants without TOD) to examine the relation of hypertension onset age and hypertensive TOD. Compared with normotensive individuals, hypertension onset at age <35 years was related to odds ratios of 2.29 (95% CI, 1.36–3.86), 2.94 (95% CI, 1.57–5.49), 1.12 (95% CI, 0.55–2.29), and 2.06 (95% CI, 1.04–4.05) for left ventricular hypertrophy, coronary calcification, albuminuria, and diastolic dysfunction, respectively. In contrast, hypertension onset at age ≥45 years was not related to increased odds of TOD. Our findings emphasize the importance of assessing age of hypertension onset in hypertensive patients to identify high-risk individuals for preventing hypertensive complications. (*Hypertension*. 2019;74:305-312. DOI: 10.1161/HYPERTENSIONAHA.119.13069.)

• [Online Data Supplement](#)

Key Words: blood pressure ■ cardiovascular diseases ■ hypertension ■ follow-up studies ■ risk factors

Although hypertension is a well-known risk factor for cardiovascular disease (CVD), the impact of age of hypertension onset on CVD risk has not been widely studied. Recent data from the Framingham Heart Study suggest that early onset hypertension is associated with a considerably greater risk for CVD mortality compared with hypertension that begins later in life.^{1–3} In addition, early onset, and not late onset hypertension, in parents is also strongly associated with hypertension in offspring.¹

Target end-organ damage (TOD) is a common complication of hypertension, which considerably increases the risk of incident overt CVD, even in well-controlled hypertension.^{4–10} Furthermore, regression of TOD has been associated with lower likelihoods of CVD morbidity and mortality, independent of blood pressure (BP) lowering in persons with hypertension.¹¹ Although early onset hypertension has been shown to increase the risk of CVD death,¹ it remains unclear if early onset hypertension also predisposes to TOD already by midlife. This information could be useful for understanding

the disease mechanisms through which early onset hypertension leads to manifest CVD. In addition, these data could be used to improve CVD risk prediction and guidance on antihypertensive therapy in patients with early onset hypertension.

Our objective was to determine the relation of hypertension onset age with hypertensive TOD in middle-aged individuals. We assessed the association of hypertension onset age with presence of left ventricular hypertrophy (LVH), coronary calcification, albuminuria, and left ventricle diastolic dysfunction in 2680 CARDIA study (Coronary Artery Risk Development in Young Adults) study participants aged 43 to 55 years. CARDIA is a large cohort study drawn from the general population that includes individuals with varying ethnic backgrounds. The participants underwent 8 follow-up examinations over a timespan of up to 31 years. A particular strength of this cohort for exploring the association between age of hypertension onset and TOD is that nearly all participants were free from hypertension at baseline, which enabled accurate determination of hypertension onset age. We hypothesized

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that early onset hypertension associates more strongly than late onset hypertension with hypertensive TOD.

Methods

Study Sample

Our study sample included participants of the prospective CARDIA cohort study. The CARDIA study was designed to examine the risk factors and development of CVD in young adults who were aged 18 to 30 years (mean age, 25±4 years) at baseline.¹² All data and materials of the CARDIA study have been made publicly available at the National Institutes of Health's Biologic Specimen and Data Repository Information Coordinating Center and can be accessed at <https://biolincc.nhlbi.nih.gov/studies/cardia/>.

The CARDIA cohort consists of 5115 participants who were recruited between 1985 and 1986 in 4 centers in Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA. The participants were chosen as evenly as possible regarding to age, sex, race, and education. Further details of the CARDIA study and its sampling have been published previously.¹² We considered the 3499 CARDIA participants who attended examination cycle 8 in 2010 to 2011. Participants who had missing covariates or TOD measurements at cycle 8 (n=819) were excluded, resulting in a final sample of 2680. Informed consent was obtained from all participants, and the study was approved by all institutional committees of each participating center.

Clinical Evaluations and Measurements

Follow-up examinations were performed 8 times in 1985 to 1986, 1987 to 1988, 1990 to 1991, 1992 to 1993, 1995 to 1996, 2000 to 2001, 2005 to 2006, and 2010 to 2011. At examinations 1 through 6, BP was measured at each visit 3× using a random zero mercury sphygmomanometer between the first and sixth examinations. All personnel collecting BP data were trained and certified centrally at each examination cycle, including pretraining and posttraining tests. For quality control, BP measurements were carried out in duplicates. No distinct differences were observed between centers when comparing technician-specific single-point histograms.¹³ A validated Omron model HEM907XL oscillometric monitor¹⁴ was used at the seventh and eighth examinations for BP measurements. BP was 3× measured from the right arm of sitting participants after 5 minutes of quiet rest by a trained technician at all examinations. Differences between auscultatory and oscillometric measurements were corrected by calibrating the oscillometric values to sphygmomanometer measures as previously described.¹⁵ We used the average of the second and third measurements as the BP at each cycle.

In addition to echocardiography, all participants underwent measurements for coronary artery calcification and urine albumin-creatinine ratio at examination cycle 8. Echocardiographic measurements were performed according to a standardized protocol across all study centers using 2-dimensionally guided M-mode and Doppler echocardiography. All echocardiograms were read centrally by experienced echocardiographic sonographers. Left ventricular mass (LVM) and peak velocity flow in early and late diastole were calculated from the echocardiograms as previously described.¹⁶ LVM index was calculated by dividing LVM by body surface area ($0.007184 \times \text{weight [kg]}^{0.425} \times \text{height [cm]}^{0.725}$). Coronary artery calcification levels were measured with a cardiac multidetector computed tomography.¹⁷ All images were evaluated centrally, and the Agatston score was calculated for each participant.¹⁸ Urinary creatinine and albumin levels were measured using a single, untimed spot urine sample, and the samples were analyzed centrally, as described previously.¹⁹

Current smoking was obtained with self-administrated questionnaires. Height and weight were measured from participants with light clothing. Total cholesterol, HDL (high-density lipoprotein) cholesterol, and serum glucose were measured from fasting samples by standard enzymatic methods.^{12,20} Diabetes mellitus was defined by serum fasting glucose ≥ 7 mmol/L or use of antihyperglycemic

medication. Information on use of antihypertensive medication was collected by self-report and from medications brought on-site at each examination.

Exposure and Outcome Variables

We used age of hypertension onset as the exposure variable. Assessment of hypertension onset was based on all available BP measurements performed at 8 serial examinations from 1985 through 2011. We defined hypertension onset as BP $\geq 140/90$ mmHg or use of antihypertensive medication on 2 consecutively attended examinations. We used this definition to reduce variation between single observed high BP measurements to demonstrate a lasting change in BP. In accordance with previous studies, we defined the age of hypertension onset as the age at the first examination on which the criteria for hypertension was met.^{1,21} We divided the participants into 4 groups according to their age of hypertension onset: <35 years, 35 to 44 years, ≥ 45 years, or no hypertension.

We used LVH, left ventricle diastolic dysfunction, coronary calcification, and albuminuria at examination 8 as the outcome variables. We defined LVH as increased LVM index >115 g/m² in men and >95 g/m² in women.²² Left ventricle diastolic dysfunction was defined as a ratio between peak velocity flow in early and late diastole of >2.0 or <0.8 .²² We defined coronary artery calcification as an Agatston score of ≥ 100 ²³ and albuminuria as urine albumin-creatinine ratio >30 mg/g.²⁴

Statistical Analyses

We assessed the sample characteristics at examination 8 in the whole sample and in subgroups by hypertension onset age. We compared the participants' characteristics and measured TOD using a χ^2 test for categorical variables and ANOVA for continuous variables. Because of a skewed distribution, we log-transformed urine albumin-creatinine ratio before analyses. We also compared the study sample baseline characteristics with CARDIA study participants who were excluded from the analyses. Using univariable and multivariable logistic regression models, we examined the relation of hypertension onset age groups and presence of TOD using a case (presence of TOD) versus control (no TOD) design with those who did not develop hypertension as the referent group. We used case-control study design, instead of a prospective approach, which allowed for the exposure variable to consistently precede the outcome variable in timing. We performed a sensitivity analysis without individuals who were hypertensive at exam 8. In the main analysis, these individuals were classified nonhypertensive as a result of not having hypertension on 2 consecutive examinations. We also examined the association between age of hypertension onset and number of TODs (0, 1, or ≥ 2) using multinomial logistic regression model. We adjusted the multivariable analyses for age, sex, body mass index, total serum cholesterol, HDL cholesterol, smoking status, use of antihypertensive medication, diabetes mellitus, race, and systolic BP. The covariates were drawn from examination 8. We also performed a supplementary analysis by adjusting for covariates drawn from the baseline examination instead of examination 8. Diabetes mellitus was not included as a covariate in this analysis because of the low number of diabetic individuals at baseline. We tested for a linear trend in odds ratios across categories of age at hypertension onset. We carried out all analyses using SAS software version 9.4 (SAS Institute, Cary, NC). A 2-tailed $P < 0.05$ was considered statistically significant.

Results

The characteristics of the whole study sample (mean age, 50 years; 57% women) and in groups according to hypertension onset age are presented in Table 1. In general, the participants' CVD risk factors, such as diabetes mellitus, smoking prevalence, body mass index, and HDL cholesterol, improved with increasing age of hypertension onset. Individuals with early onset hypertension were more likely to be men. Although some differences were statistically significant, we observed

Table 1. Sample Characteristics

Characteristic	Age of Hypertension Onset					P Value
	All	<35 y	35–44 y	≥45 y	No Hypertension	
N	2680	94	251	136	2199	
Age, y (SD)	50.1 (3.6)	49.8 (3.4)	49.9 (3.5)	53.3 (1.8)	49.9 (3.6)	<0.001
No. of women, %	1525 (56.9)	51 (54.3)	150 (59.8)	83 (61.0)	1241 (56.4)	0.52
BMI, kg/m ² (SD)	25.2 (5.5)	28.1 (6.2)	28.5 (6.2)	27.4 (5.7)	24.6 (5.2)	<0.001
Current smoker, %	447 (16.7)	18 (19.2)	46 (18.3)	24 (17.7)	359 (16.3)	0.75
Cholesterol, mmol/L (SD)	5.0 (0.9)	4.8 (1.0)	4.8 (1.0)	4.8 (1.0)	5.0 (0.9)	0.0002
HDL cholesterol, mmol/L (SD)	1.5 (0.5)	1.4 (0.6)	1.38 (0.4)	1.43 (0.5)	1.5 (0.5)	<0.001
Systolic blood pressure, mm Hg (SD)	118 (15.3)	128 (15.6)	127 (18.7)	126 (19.0)	117 (13.8)	<0.001
Diastolic blood pressure, mm Hg (SD)	73.8 (10.8)	80.7 (9.9)	79.7 (12.4)	78.4 (11.8)	72.5 (10.2)	<0.001
Use of antihypertensive medication, %	686 (25.6)	83 (88.3)	226 (90.0)	124 (91.2)	253 (11.5)	<0.001
Diabetes mellitus, %	240 (9.0)	27 (28.7)	51 (20.3)	23 (16.9)	139 (6.3)	<0.001
Nonhispanic black, %	1280 (47.8)	71 (75.5)	189 (75.3)	74 (54.4)	946 (43.0)	<0.001

Sample characteristics were drawn from examination 8. BMI indicates body mass index; and HDL, high-density lipoprotein.

no major differences in the study sample baseline characteristics compared with CARDIA study participants who were excluded from the analyses (Table S1 in the [online-only Data Supplement](#)). A total of 2, 3, 4, 5, 6, 7, and 8 BP measurements were available for 14, 22, 59, 96, 182, 373, and 1934 participants, respectively.

The mean level and prevalence of hypertensive TOD according to hypertension onset age are shown in Table 2. In general, the level and prevalence of LVH, coronary calcification, albuminuria, and left ventricle diastolic dysfunction increased with decreasing age of hypertension onset. Odds of TOD increased linearly in unadjusted models ($P < 0.005$ for all) but not in the multivariable adjusted models ($P > 0.11$ for all). Table 3 shows the odds of TOD by age group of hypertension onset. In unadjusted models, individuals with hypertension onset at age <35 years had odds ratios of 3.35 (95% CI, 2.16–5.20), 4.33 (95% CI, 2.61–7.18), 3.49 (95% CI, 1.91–6.36), and 2.17 (95% CI, 1.22–3.85) for LVH, coronary calcification, albuminuria, and left ventricle diastolic dysfunction compared

with individuals without hypertension, respectively. In models adjusted for common TOD risk factors determined at examination 8, including systolic BP, the respective odds ratios were 2.29 (95% CI, 1.36–3.86), 2.94 (95% CI, 1.57–5.49), 1.12 (95% CI, 0.55–2.29), and 2.06 (95% CI, 1.04–4.05); Table 3. The results were similar when covariates were drawn from the baseline examination (Table S2). In fact, our findings on the adverse nature of early onset hypertension were even more evident when participants with new-onset hypertension at the last examination, who were classified nonhypertensive, were excluded (Table S3).

Prevalence of TOD (0, 1, or ≥2 damaged organs) in subgroups by hypertension onset age is shown in Figure 1. Nonhypertensive participants had the lowest prevalence of TOD (23.7%; 4.6% with TOD in ≥2 organs). About 59.5% of individuals with hypertension onset at age <35 years had hypertensive TOD and 24.5% had damage in multiple organs. The odds of having TOD in 1 or ≥2 organs by hypertension onset age is shown in Table 4. Early onset hypertension was

Table 2. Prevalence of Hypertensive Organ Damage According to Hypertension Onset Age

Hypertension Onset Age	Hypertension Onset Age					P Value
	All	<35 y	35–44 y	≥45 y	No Hypertension	
N	2680	94	251	136	2199	
LVMI, g/m ² (SD)	85.2 (21.3)	97 (27.2)	94 (27.1)	92 (22.3)	83 (19.7)	<0.001
LVH, n (%)	444 (16.6)	33 (35.1)	73 (29.1)	32 (23.5)	306 (13.9)	<0.001
CAC-score, AU (SD)	40.2 (205)	215 (743)	62 (177)	80 (210)	28 (142)	<0.001
Increased CAC-score, n (%)	235 (8.8)	22 (23.4)	40 (15.9)	28 (20.6)	145 (6.6)	<0.001
UACR, median (IQR)	4.79 (3.31–8.38)	6.67 (4.03–15.57)	7.27 (4.51–16.95)	5.09 (3.56–8.38)	4.55 (3.19–7.68)	<0.001
Increased UACR, n (%)	165 (6.2)	14 (14.9)	36 (14.3)	10 (7.4)	105 (4.8)	<0.001
E/A ratio (SD)	1.30 (0.4)	1.14 (0.4)	1.18 (0.3)	1.20 (0.4)	1.33 (0.4)	<0.001
Abnormal E/A ratio, n (%)	239 (8.9)	15 (16.0)	31 (12.4)	16 (11.8)	177 (8.1)	0.005

AU indicates Agatston units; CAC, coronary artery calcification; E/A ratio, ratio between E wave peak velocity flow in early diastole and A wave peak velocity flow in late diastole; IQR, interquartile range; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; and UACR, urine albumin/creatinine ratio.

Table 3. Odds of Hypertensive Organ Damage According to Hypertension Onset Age

Hypertension Onset Age	LVH		Coronary Calcification		Albuminuria		Diastolic Dysfunction	
	n/N	OR (95% CI)	n/N	OR (95% CI)	n/N	OR (95% CI)	n/N	OR (95% CI)
Unadjusted model								
<35	33/94	3.35 (2.16–5.20)*	22/94	4.33 (2.61–7.18)*	14/94	3.49 (1.91–6.36)*	15/94	2.17 (1.22–3.85)†
35–44	73/251	2.54 (1.88–3.42)*	40/251	2.69 (1.84–3.92)*	36/251	3.34 (2.23–5.00)*	31/251	1.61 (1.07–2.42)‡
≥45	32/136	1.90 (1.26–2.88)†	28/136	3.67 (2.35–5.75)*	10/136	1.58 (0.81–3.10)	16/136	1.52 (0.88–2.62)
No hypertension	306/2199	1.00	145/2199	1.00	105/2199	1.00	177/2199	1.00
Multivariable-adjusted model								
<35	33/94	2.82 (1.67–4.74)*	22/94	3.15 (1.69–5.86)*	14/94	1.49 (0.73–3.02)	15/94	2.04 (1.04–3.99)‡
35–44	73/251	2.07 (1.40–3.08)*	40/251	1.94 (1.17–3.23)‡	36/251	1.63 (0.96–2.76)	31/251	1.58 (0.93–2.69)
≥45	32/136	1.52 (0.92–2.51)	28/136	1.49 (0.83–2.65)	10/136	0.84 (0.39–1.81)	16/136	1.43 (0.74–2.76)
No hypertension	306/2199	1.00	145/2199	1.00	105/2199	1.00	177/2199	1.00
Multivariable+SBP-adjusted model								
<35	33/94	2.29 (1.36–3.86)†	22/94	2.94 (1.57–5.49)*	14/94	1.12 (0.55–2.29)	15/94	2.06 (1.04–4.05)‡
35–44	73/251	1.67 (1.12–2.48)‡	40/251	1.83 (1.10–3.05)‡	36/251	1.25 (0.74–2.09)	31/251	1.59 (0.93–2.73)
≥45	32/136	1.23 (0.74–2.03)	28/136	1.41 (0.79–2.52)	10/136	0.62 (0.29–1.34)	16/136	1.44 (0.75–2.79)
No hypertension	306/2199	1.00	145/2199	1.00	105/2199	1.00	177/2199	1.00

Multivariable-adjusted model is adjusted for age, sex, body mass index, total serum cholesterol, HDL cholesterol, smoking status, use of antihypertensive medication, race, and diabetes mellitus. Trend test *P* value for ORs across age groups for LVH, coronary calcification, albuminuria, and diastolic dysfunction were <0.0001, <0.0001, <0.0001, and 0.005, respectively. The corresponding *P* values were 0.009, 0.068, 0.56, and 0.16 for the multivariable-adjusted models and 0.12, 0.11, 0.68, and 0.16 for the multivariable+SBP-adjusted models, respectively. HDL indicates high-density lipoprotein; n/N, number of individuals with organ damage/number of individuals in category; LVH, left ventricular hypertrophy; OR, odds ratio; and SBP, systolic blood pressure.

**P*<0.001.

†*P*<0.01.

‡*P*<0.05.

particularly strongly related to having TOD in ≥2 organs (*P*<0.001; Table 4). Figure also illustrates the adjusted odds of having TOD in 1 or ≥2 organs by hypertension onset age subgroups.

Discussion

Hypertension onset at age <35 years of age was associated with significantly increased odds of LVH, coronary calcification, and left ventricular diastolic dysfunction in middle-aged individuals whereas onset at ≥45 years of age was not. The odds of TOD for all aforementioned organs were always greatest in the group with hypertension onset at under 35 years of age. About 24.5% of the individuals in this group had concurrent TOD in 2 or more organs.

To our knowledge, no previous studies have examined the relation of hypertension onset age and conventional hypertensive TOD. Limited data also exist on the impact of hypertension onset age on risk of overt CVD. The first results on this domain are from a 1987 study, which examined the risk of CVD events in patients drawn from 34 general practices.³ In this study, hypertension onset at age 40 to 49 years was related to a notable 5.2-fold odds of CVD events compared with normotensives of similar age. In contrast, the corresponding odds ratio was only 1.2 for individuals with hypertension onset at age 60 to 65 years. However, this study had some limitations, such as lack of adjustment for many conventional CVD risk factors, including cholesterol

and diabetes mellitus. In addition, age at hypertension diagnosis, instead of objectively defined age of onset based on serial measurements, was used as the exposure variable. These limitations were addressed in a recent publication based on Framingham Heart Study Original cohort data.^{1,2} In this study, we observed that objectively diagnosed early onset hypertension (onset at age <55 years) was related to 2.2-fold odds of CVD death compared with individuals who never developed hypertension as compared with only 1.5-fold odds in individuals who developed hypertension at age ≥65 years. Overall, these prior results demonstrate that early onset hypertension is a strong predictor of CVD outcomes in later life. The results of the current study expand these previous findings by demonstrating that early onset hypertension is also related to a high risk of TOD already by midlife. Given that TOD increases the risk of overt CVD several fold in hypertensive patients,^{4–10} our findings could have considerable clinical importance as they highlight the need of adequate BP control particularly in young hypertensive patients.

No prior studies have directly compared the differences of age of hypertension onset and age at hypertension diagnosis. For several other diseases, such as ankylosing spondylitis and dementia, a considerable delay exists between the time of first symptoms and time of diagnosis.^{25,26} However, these results may not be generalizable to hypertension, which is usually a symptomless condition. In this study, we used objective BP measurements conducted at regular follow ups to define age

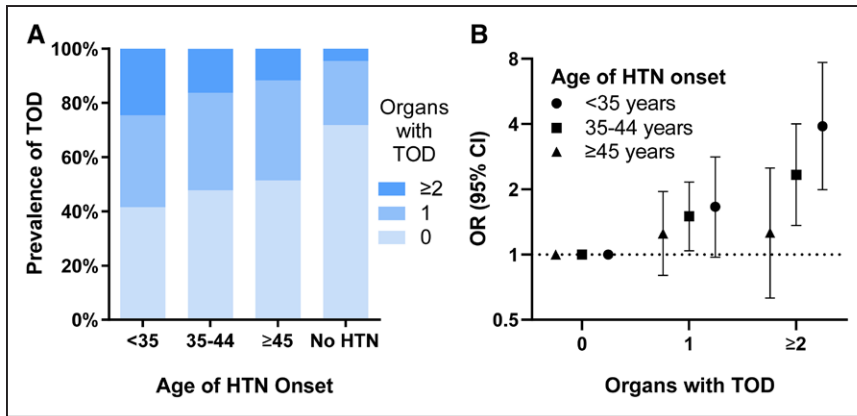


Figure. Proportion of individuals with 0, 1, or ≥2 types of target organ damage by hypertension onset age (A). Odds of having 0, 1, or ≥2 organs with damage by hypertension onset age (B). HTN indicates hypertension; OR, odds ratio; and TOD, target end-organ damage.

of hypertension, in contrast to self- or clinician-reported age of hypertension diagnosis. We think this to be a more accurate method for determining the actual age of hypertension onset. However, additional studies are needed to assess the differences between self-reported and objectively assessed age of hypertension onset.

In previous studies, Franks et al²⁷ have shown that childhood hypertension increases the risk of premature death from endogenous causes. However, in this study, BP in childhood on a continuous scale did not significantly predict premature death. Several other studies have also observed an association for systolic BP, diastolic BP, and BP trajectories with LVM and LVH in children and young adults.²⁸⁻³¹ Similar results have also been reported concerning carotid artery intima-media thickness.^{30,32-34} However, these studies used repeatedly measured BP as the exposure variable instead of hypertension onset age.

Apart from classical markers of hypertensive TOD, such as LVH, the relation of hypertension onset age and cognitive decline has been assessed in the oldest old. A single recent study by Corrada et al³⁵ suggested that hypertension onset at age >80 years could paradoxically be protective of incident dementia in a cohort of 559 individuals aged >90 years. This association remained even after evaluating the potential for survival bias. Although the main finding of this study was only borderline significant ($P=0.04$), it remains plausible that hypertension onset at a high age could be protective against some adverse outcomes, in contrast to hypertension that begins in mid- or late life. However, this finding needs replication in an external population before any definitive conclusions can be made.

Age of hypertension onset has also been studied in the context of hypertension risk in the offspring. Family studies have previously shown that BP is a highly heritable trait.³⁶ Furthermore, early onset hypertension in particular seems to have a strong genetic component.³⁷⁻⁴² Apart from heritability estimates, recent epidemiological studies have also provided point estimates for the risk of hypertension in individuals categorized by age of parental hypertension onset. In the Johns Hopkins Precursor Study with a sample of 1160 male physicians, self-reported early onset (at age ≤55 years) hypertension in both parents imparted a 6.2-fold higher adjusted risk for the development of hypertension throughout adult life compared with individuals whose parents never developed hypertension.²¹ In the Framingham Heart Study Offspring cohort, objectively determined early onset hypertension (at age ≤55 years) in both parents was related to 3.5-fold odds of hypertension.¹ Interestingly, early onset hypertension in grandparents also seems to raise the risk for hypertension in grandchildren, even after adjusting for early onset hypertension in parents and lifestyle factors.^{1,43} These findings, together with the observed increased CVD risk related to early onset, highlight the importance of assessing both parental and grandparental age of hypertension onset in hypertensive patients.

Our study has several strengths. Our large study sample was drawn from the general population. In addition, the participants were followed up for up to 31 years over 8 follow-up examinations conducted at regular intervals. The participants were relatively young at baseline and, therefore, only a small number of participants had developed hypertension at the start of the study. Therefore, the study sample was optimal for assessing the relation of hypertension onset age with

Table 4. Odds of Having 0, 1, or ≥2 Organs With Organ Damage by Hypertension Onset Age

Hypertension Onset Age	TOD in 0 Organs		TOD in 1 Organ		TOD in ≥2 Organs	
	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)
<35 y (n=94)	39	1.00	32	1.66 (0.97-2.82)	23	3.91 (1.99-7.69)*
35-44 y (n=251)	120	1.00	90	1.50 (1.04-2.16)‡	41	2.33 (1.36-4.00)†
≥45 y (n=136)	70	1.00	50	1.25 (0.80-1.95)	16	1.26 (0.63-2.51)

Models are adjusted for age, sex, body mass index, total serum cholesterol, HDL cholesterol, smoking status, systolic blood pressure, use of antihypertensive medication, race, and diabetes mellitus. Organ damage sum (0, 1, or ≥2) was defined as the total number of organs with damage. HDL, high-density lipoprotein; OR, odds ratio; and TOD, target organ damage.

* $P<0.001$.

† $P<0.01$.

‡ $P<0.05$.

hypertensive TOD. In addition to strengths, we also recognize some limitations of this study. About 68.4% of individuals who participated in the baseline examination took part in examination 8. However, there were no clinically significant differences between individuals who were included and excluded in this analysis (Table S1). We defined hypertension onset age by objectively measured elevated BP or use of antihypertensive medication on 2 consecutively attended examinations to reduce variation based on only 1 measurement and to represent a durable change in BP. However, we were not able to include the intensity of the antihypertensive therapy in the analyses despite recognizing that this could also affect the risk of hypertensive TOD.

Finally, the overall exposure time to hypertension is most likely a key contributing factor in the relation of hypertension onset age and hypertensive TOD. Notwithstanding potentially similar effects, we recognize that duration of exposure to hypertension is a distinct entity from age of hypertension onset, given that exposure from age 20 to 40 years is not the same as exposure from age 70 to 90 years. Accordingly, prior reports have shown that the effect of exposure time on CVD risk can vary depending on the patient's age and that developing hypertension at older ages may even protect against dementia.^{35,44} In addition, hypertension onset age, but not hypertension duration, has a strong impact on the heritability of hypertension.¹ Unfortunately, the differential effects of hypertension age of onset and hypertension exposure time on CVD risk cannot be assessed in this study sample as the CARDIA participants had a narrow age range at baseline. As a result, exposure time is nearly equivalent to age of onset in CARDIA because of the narrow age range of the participants, precluding a meaningful analysis for comparing the effects of these 2 entities on TOD.

Perspectives

Our findings suggest that hypertensive TOD is robustly associated with early onset hypertension already by midlife. Hypertensive TOD is a well-known and robust risk factor for CVD events such as myocardial infarction and stroke, independent of BP.^{7–10} Our findings further emphasize the importance of assessing age of hypertension onset in hypertensive patients to identify individuals at high risk of developing TOD and, as a result, to prevent TOD and overt CVD. Previous studies have shown that long-term cumulative BP levels are also associated with increased risk of CVD, independent of single occasion BP measurements.^{45,46} These results are in line with previous data on the impact of repeated BP measurements in childhood, adolescence, and young adulthood, to some conventional TOD.^{28–34} However, in this study, we focus on the differences in odds of TOD and sum of TODs by subgroups according to age at hypertension onset. In addition, determining age of hypertension onset could offer a simple method for clinicians to assess a patient's overall risks associated with exposure to hypertension. Our results, in conjunction with previous research,^{1–3} suggest that physicians should be aggressive when diagnosing and treating young hypertensive patients who often remain undertreated.^{47,48} Physicians should consider initiating antihypertensive treatment in younger hypertensive patients when they do not respond to lifestyle changes, even if their estimated short-term CVD risk

remains moderate. Further studies are still needed to elucidate the potential disease mechanisms of early onset hypertension.

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Disclosures

None.

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Novelty and Significance

What Is New?

- Prior studies have demonstrated that hypertension onset at an early age is strongly related to cardiovascular mortality and risk of hypertension in offspring.
- Whether early onset hypertension also promotes the development of target end-organ damage, even by midlife, has remained unknown.

What Is Relevant?

- Early hypertension onset age is associated with increased risk of left ventricular hypertrophy, coronary calcification, and left ventricle diastolic dysfunction, compared with late onset hypertension.

Summary

Our findings emphasize the importance of assessing age of hypertension onset in patients with hypertension to identify high-risk individuals and to prevent hypertensive complications such as hypertensive target organ damage and overt cardiovascular disease.