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EDITORIAL COMMENT

Early-Onset Hypertension

Under-Recognized, Under-Treated, and Under-Estimated in Risk*

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High blood pressure remains a leading modifiable risk factor for cardiovascular disease (CVD) in both the young and the old (1,2). Surprisingly few studies have examined the age at which hypertension *begins* and its relation to later-life risk for CVD outcomes (3-8). The evidence to date would suggest that an early age of hypertension onset is associated with not only increased risk of CVD, but also transmission to offspring, whereas hypertension onset in later life is more benign in nature (3-8). Importantly, prior analyses have involved predominantly retrospective case-control designs that may be subject to selection or recall bias and are also limited in their ability to establish a temporal relationship between the exposure and outcome. In this issue of the *Journal*, Wang et al. (9) effectively advance our understanding by investigating the prognosis of early compared with late hypertension onset in relation to CVD risk in the setting of a large cohort study design.

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In their analyses of hypertension onset, Wang et al. (9) used data from the prospective Kailuan cohort, which includes 101,510 Chinese community-dwelling participants who were followed biennially between 2006 and 2017. For this study, the authors used a sample of 19,887 cases with new-onset hypertension and an equal number of age- and sex-matched control subjects without hypertension. The follow-up period for the cases started at the time of hypertension onset, and the follow-up period for the control subjects started during the same year when incident cases were identified. The primary CVD outcomes included myocardial infarction, stroke, and all-cause mortality. The researchers used Cox proportional hazards regression models to determine the risk of outcomes in subgroups according to hypertension-onset age, compared with those without hypertension. The authors observed that individuals with hypertension-onset age ≤45 years carried the highest risk for CVD (hazard ratio [HR]: 2.26; 95% confidence interval [CI]: 1.19 to 4.30) and all-cause mortality (HR: 2.59; 95% CI: 1.32 to 5.07). The risk estimates of both CVD and all-cause mortality consistently decreased with each incrementally later age decade of hypertension onset. Consequently, participants with hypertension-onset age ≥65 years had the lowest hazards of CVD (HR: 1.33; 95% CI: 1.04 to 1.69) and all-cause mortality (HR: 1.29; 95% CI: 1.11 to 1.51).

This report by Wang et al. (9) has several strengths. Perhaps most important, it is the first time-to-event cohort study to assess the relation between age of hypertension onset and adverse outcomes. Additional reliability is offered by the substantially large cohort size, with the number of outcome events including 1,672 cases of incident CVD and a total of 2,008 deaths. Importantly, the researchers were also able to objectively determine the exact timing between age of hypertension onset and the incidence of events in the participants. There were also some

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limitations that were noted by the authors. The mean follow-up duration for participants studied was relatively short, at 6.5 years. Furthermore, the initial cohort consisted of employees of a single company, and only 65.3% agreed to participate in the study (10), contributing to some level of potential selection bias. Additionally, estimated hazards in the multivariable models were adjusted for fasting blood glucose but not for the use of antihyperglycemic medication, which could lead to an underestimation of diabetes-related risks. Similarly, blood pressure levels during and prior to the outcome assessments were not considered. Notwithstanding these limitations, the strengths of this study overall outweigh the weaknesses.

Notably, the results from the study by Wang et al. (9) are consistent with the findings of prior case-control studies (3–6). In the Framingham and the Coronary Artery Risk Development in Young Adults studies, early-onset hypertension was related to hypertension-mediated organ damage (5,6) and CVD death (4) to a greater extent than late-onset hypertension. Extending from prior work, Wang et al. (9) also demonstrate that early-onset compared with late-onset hypertension is significantly associated with greater risk of all-cause mortality. Only a few studies have examined hypertension-onset age as a risk factor for diseases other than CVD. Two previous studies with contrasting results have suggested that age of hypertension onset might be related to risk of developing dementia in the elderly (11,12). Thus, the association between hypertension-onset age and non-CVD mortality warrants further investigation.

The implications of this work are potentially far-reaching. The authors correctly speculate that assessment of hypertension-onset age could improve the overall CVD risk stratification, and that individuals with early-onset hypertension might benefit from more intensive hypertension treatment, including lifestyle interventions and antihypertensive therapy. In addition, prior research suggests that parental age of hypertension could also be used for estimating risk of hypertension in offspring (4). However, implementing assessment of hypertension-onset age into clinical practice may have its challenges. Namely, studies have mainly defined time of onset using serial blood pressure readings, which may not be available in the regular clinical setting. To address this potential barrier to pragmatic implementation of new knowledge, we recently showed that the age of hypertension onset can be reliably determined using self-report (6). Thus, use of self-report could improve the feasibility of incorporating an assessment of hypertension-onset age into clinical practice, particularly in situations where prior medical records data are not available.

In summary, Wang et al. (9) provide additional compelling evidence on the adverse effects of early-onset hypertension in a large-scale prospective cohort study. Although the rates of hypertension awareness, treatment, and control are lower among younger compared with older adults, current guidelines do not recommend using age of hypertension onset as part of a CVD risk assessment; contemporary recommendations also do not yet emphasize the importance of adequate therapy in young patients (2,13,14). Future guideline iterations could include revisions that specify treatment approaches for patients with early-onset hypertension, given their considerably greater lifetime CVD risk when compared with patients with late-onset hypertension (3–6,9).

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