Above Which Blood Pressure Level Does the Risk of Atrial Fibrillation Increase?

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Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, occurs in 1% to 2% of the general population, and its incidence is growing. Mostly because of the progressive aging of the population, the prevalence of AF is expected to double over the next 50 years. AF is a potentially devastating condition for several reasons. It portends a 5-fold risk of stroke, and ischemic strokes that occur in people with AF are often fatal or leave surviving patients generally more disabled and at higher risk of recurrences compared with other causes of stroke. AF triples the risk of heart failure, doubles the risk of dementia, and markedly increases the risk of all-cause mortality. For the above reasons, prevention of AF through appropriate control of its modifiable risk factors is a public health priority. Unfortunately, despite numerous experimental and clinical studies, the individual risk of developing AF in a given time frame is still difficult to estimate. Hypertension is a well-known modifiable risk factor for AF, although it is unclear above which blood pressure (BP) level the risk of AF definitely increases and, even more important, which target BP level should be pursued to reduce the risk of AF in treated hypertensive patients.

BP Level and the Risk of AF

In a population based, case-control study of 433 patients with incident AF and 899 controls, the risk of AF doubled in participants with systolic BP ≥150 mm Hg compared with patients with systolic BP levels of 120 to 129 mm Hg. However, this excess risk was not significant in those with systolic BP 140 to 149 mm Hg (odds ratio 1.40, 95% CI 0.93–2.09), whereas there was an increased risk of AF associated with systolic BP <120 mm Hg, consistent with a J-curve phenomenon. Conversely, in a large cohort of women enrolled in the Women’s Health Study, a continuous relation emerged between BP, even in the normal range, and the risk of incident AF during a median follow-up period of 14 years. Participants with systolic or diastolic BP values in the high-normal range according to the European Guidelines (130–139 for systolic BP, 85–89 for diastolic BP) experienced 28% and 53% excess risk of incident AF when compared with women with systolic BP <120 mm Hg or diastolic BP <65 mm Hg, respectively.

A long-term epidemiological study featured in this issue of Hypertension extends to men the direct relationship between BP and the risk of incident AF. Grundvold et al studied a group of 2014 healthy Norwegian men first scrutinized in the years 1972 to 1975. During a median follow-up period of 30 years, 270 men were hospitalized for various reasons, with available evidence of AF from hospital records. The risk of AF significantly increased in men with baseline systolic BP 128 to 138 mm Hg (third quartile) compared with men with systolic BP <128 mm Hg (bottom quartile), as well as in those with diastolic BP 80 to 86 mm Hg (second quartile) compared with men with diastolic BP <80 mm Hg (bottom quartile). Because of the long duration of follow-up, several patients (n=115) developed 1 or more conditions that put them at increased risk of AF regardless of BP levels, such as myocardial infarction, heart failure, coronary artery bypass, or diabetes mellitus. However, even after allowance for these conditions, the risk of incident AF remained significantly higher by 98% and 67% in those with systolic BP 128 to 138 or diastolic BP 80 to 86 mm Hg compared with those with BP <128/80 mm Hg, respectively.

An inherent limitation of both studies is the uncertainty regarding the impact of BP changes over time on the development of AF. Subjects with high-normal BP tend to progress to hypertension more frequently than subjects with lower BP values. Therefore, the later development of hypertension, not the initial high-normal BP status, could be the major causative factor for AF. Conen et al tried to address the issue by entering BP as a time-varying covariate in the analysis, and Grundvold et al tried to address it by making additional analyses that excluded individuals who developed hypertension at a second survey carried out in 1980 to 1982. However, some uncertainty on this aspect remains because of the potential effect of both competing risks and unmeasured confounders.

Therapeutic Implications

Taken together, the studies by Conen et al and Grundvold et al, although conducted in predominantly white populations and therefore not easily generalizable to different ethnic groups, suggest that the risk of AF is increased in subjects with BP in the high-normal range. These data generate the hypothesis that the nonpharmacological and pharmacological measures that can retard the progression from prehypertension to hypertension might also prevent the occurrence of new AF. An additional attractive hypothesis is that a more
aggressive control of BP in hypertensive patients may decrease the risk of AF. However, studies in this setting are scant. In the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT), patients randomly assigned to chlorthalidone had a mean in-trial systolic BP 3 mm Hg lower than that of patients randomly assigned to doxazosin,\textsuperscript{11} and the incidence of new AF or flutter was significantly higher in the doxazosin group than in the chlorthalidone group (odds ratio 1.35, $p = 0.02$).\textsuperscript{12}

Studies targeting different BP targets could be particularly useful in this setting. For example, in the Studio Italiano Sugli Effetti CARDIOvascolari del Controllo della Pressione Ateriosi SISTolica (Cardio-Sis) trial, 1111 treated hypertensive patients in sinus rhythm were randomly assigned to a target systolic BP of less than 140 mm Hg (usual control) or less than 130 mm Hg (tight control), and new AF was a prespecified secondary outcome of the study. At the end of a median follow-up period of 2 years, new AF occurred in 3.8% of patients in the usual control group and 1.8% of patients in the tight control group (hazard ratio 0.46, 95% CI 0.22–0.98, $p = 0.044$) (Figure).\textsuperscript{13} Because of the relatively small size of the Cardio-Sis study, the hypothesis that a tight BP control is more effective than a usual BP control for prevention of AF should be tested in larger trials.

In conclusion, there is no question that global preventive strategies are urgently needed to reduce the burden of AF. A recent report from a National Heart, Lung, and Blood Institute Workshop recommends constructing ad hoc analyses of available studies with an emphasis on AF and including AF as an outcome measure in future studies.\textsuperscript{5} Given that the risk of AF increases in individuals of both genders with BP in the prehypertension range,\textsuperscript{7,8} it is imperative that researchers make further analyses of existing databases and conduct properly designed intervention studies to clarify the relationship between BP control strategies and the risk of AF.

Sources of Funding
This study was supported in part by the Fondazione Umbra Cuore e Ipertensione (ONLUS), Perugia, Italy.

Disclosures
None.

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Hypertension. 2012;59:184-185; originally published online January 17, 2012;
doi: 10.1161/HYPERTENSIONAHA.111.187260
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/59/2/184

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