

# Risk of cardiovascular events among women with high normal blood pressure or blood pressure progression: prospective cohort study

David Conen,<sup>1</sup> Paul M Ridker,<sup>2</sup> Julie E Buring,<sup>1</sup> Robert J Glynn<sup>1</sup>

## EDITORIAL by Nash

<sup>1</sup>Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, 900 Commonwealth Avenue, Boston, MA 02215, USA

<sup>2</sup>Divisions of Preventive Medicine and Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital

Correspondence to: D Conen  
conend@uhhs.ch

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## ABSTRACT

**Objective** To compare cardiovascular risk among women with high normal blood pressure (130-9/85-9 mm Hg) against those with normal blood pressure (120-9/75-84 mm Hg) and those with baseline hypertension.

**Design** Prospective cohort study.

**Setting** Women's health study, United States.

**Participants** 39 322 initially healthy women classified into four categories according to self reported baseline blood pressure and followed for a median of 10.2 years.

**Main outcome measures** Time to cardiovascular death, myocardial infarction, or stroke (major cardiovascular event—primary end point); progression to hypertension.

**Results** 982 (2.5%) women developed a major cardiovascular event, and 8686 (30.1%) women without baseline hypertension progressed to hypertension. The age adjusted event rate for the primary end point was 1.6/1000 person years among women with normal blood pressure, 2.9/1000 person years among those with high normal blood pressure, and 4.3/1000 person years among those with baseline hypertension. Compared with women with high normal blood pressure (reference group), those with normal blood pressure had a lower risk of a major cardiovascular event (adjusted hazard ratio 0.61, 95% confidence interval 0.48 to 0.76) and of incident hypertension (0.42, 0.40 to 0.44). The hazard ratio for a major cardiovascular event in women with baseline hypertension was 1.30 (1.08 to 1.57). Women who progressed to hypertension (reference group) during the first 48 months of the study had a higher cardiovascular risk than those who remained normotensive (adjusted hazard ratio 0.64, 0.50 to 0.81). Women with high normal blood pressure at baseline who progressed to hypertension (reference group) had similar outcome rates to women with baseline hypertension (adjusted hazard ratio 1.17, 0.88 to 1.55).

**Conclusion** The cardiovascular risk of women with high normal blood pressure is higher than that of women with normal blood pressure. The cardiovascular risk of women who progress to hypertension is increased shortly after a diagnosis of hypertension has been made.

**Trial registration** Clinical trials NCT00000479.

## INTRODUCTION

Hypertension is defined as a systolic blood pressure of at least 140 mm Hg or a diastolic blood pressure of at least 90 mm Hg. However, cardiovascular risk is directly associated with blood pressure across a much wider spectrum of blood pressure levels, and no evidence of a threshold exists down to 115/75 mm Hg.<sup>1,2</sup> Little evidence is available about the risk of

cardiovascular events in people whose blood pressure levels progress and who newly develop hypertension.

People with blood pressure levels in the normal and high normal range have a substantial risk of developing hypertension over a short term period of four years.<sup>3</sup> The cumulative lifetime risk of developing hypertension approaches 90% in a Western population.<sup>4</sup>

Strategies to prevent hypertension in people with normal blood pressure could have a substantial impact on public health. Unfortunately, published guidelines for the management of people with hypertension in Europe and the United States have adopted different classification schemes for patients with blood pressure levels considered to be normal.<sup>5,6</sup> We therefore determined the long term outcome with regard to cardiovascular disease and progression to hypertension in a large cohort of initially healthy women with a wide range of blood pressures.

## METHODS

### Participants

Participants were taken from the women's health study and were female health professionals in the United States who were 45 years or older and free of cardiovascular disease and other major illnesses. We used follow-up information starting from randomisation in 1993 to the end of the trial on 31 March 2004. Information on baseline variables was collected with mailed questionnaires, and follow-up questionnaires were sent every six months during the first year and every 12 months thereafter. Follow-up was 97.2% complete for morbidity and 99.4% complete for mortality. The study population consisted of all 39 322 women with complete information about blood pressure, history of hypertension, and antihypertensive treatment. We analysed incident hypertension among 28 863 (73.4%) women without hypertension at baseline. The median follow-up was 10.2 years.

### Study variables

Blood pressure at randomisation was self reported. We classified women into four predefined blood pressure categories: below 120 mm Hg for systolic pressure and 75 mm Hg for diastolic pressure (optimal), 120-9 mm Hg for systolic pressure or 75-84 mm Hg for diastolic pressure (normal), 130-9 mm Hg for systolic pressure or 85-9 mm Hg for diastolic pressure (high normal), and established hypertension. We defined established hypertension as self reported history of hypertension, taking antihypertensive treatment, or blood pressure

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levels of at least 140 mm Hg for systolic pressure or 90 mm Hg for diastolic pressure.

#### Ascertainment of cardiovascular outcome variables

We reviewed the medical records of all women who reported a myocardial infarction, stroke, or coronary revascularisation. We confirmed that death was from cardiovascular causes on the basis of autopsy records, death certificates, medical records, or information obtained from family members.

#### Definition of incident hypertension

We defined incident cases of hypertension for women without hypertension at baseline as meeting at least one of the following criteria: self report of a new diagnosis by a physician of hypertension; self report of taking antihypertensive treatment; or self reported blood pressure of at least 140 mm Hg for systolic pressure or 90 mm Hg for diastolic pressure.

#### Statistical analysis

The primary cardiovascular outcome variable was a composite of myocardial infarction, stroke, and death from cardiovascular causes. We also analysed the individual components, coronary revascularisation, and death from any cause as secondary variables.

*Blood pressure category and cardiovascular events*—We calculated age adjusted incidences per 1000 person years stratified by blood pressure category for the primary and all secondary outcome variables. We constructed Cox proportional hazards models to calculate hazard ratios for the comparison of event rates in the four blood pressure categories. We chose the high normal blood pressure category as the reference group. We adjusted the models for age, smoking, history of diabetes, body mass index, history of hypercholesterolaemia, exercise, alcohol consumption, educational level, and randomised treatment assignment.

*Blood pressure category and progression to hypertension*—We calculated age adjusted incidences per 1000 person years for the development of incident hypertension among women without hypertension at baseline, stratified by blood pressure category. We constructed Cox proportional hazards models to calculate the adjusted blood pressure category specific hazard ratios for incident hypertension. Women with high normal blood pressure constituted the reference group. We adjusted this model for the same variables described above.

*Blood pressure progression and cardiovascular events*—We then categorised women into the following categories: women without baseline hypertension who did not develop hypertension during the first 48 months of follow-up, women with baseline hypertension, and women without baseline hypertension who developed hypertension during the first 48 months of follow-up. We constructed Cox proportional hazards models to compare the hazard ratios for developing a primary cardiovascular outcome event between these newly created categories. We adjusted this model for age, smoking, diabetes, body mass index, and alcohol

consumption at 48 months and for baseline history of hypercholesterolaemia, exercise, educational level, and randomised treatment assignment.

## RESULTS

At baseline, 10 459 (26.6%) of the study participants had hypertension, 4988 (12.7%) had high normal blood pressure, 11 326 (28.8%) had normal blood pressure, and 12 549 (31.9%) had optimal blood pressure. Increasing blood pressure was associated with increasing age and body mass index and a higher prevalence of diabetes and hypercholesterolaemia.

#### Blood pressure category and cardiovascular events

After 10.2 years of follow-up, 982 confirmed major cardiovascular events had occurred among 39 322 women. Women with hypertension at baseline had the highest event rate (4.32 major cardiovascular events per 1000 person years). We saw a strong and consistent decrease in event rates down to the optimal blood pressure category among all primary and secondary outcomes.

Multivariable Cox proportional hazards models only slightly attenuated the strong trend across blood pressure categories (table 1). Women with normal blood pressure at baseline had a 39% lower risk of having a major cardiovascular event compared with those with high normal blood pressure, and those with optimal blood pressure at baseline had a 49% lower risk. The risk of women with established hypertension at baseline was 30% higher.

Women with hypertension had a substantially higher risk of stroke than women with high normal blood pressure (hazard ratio 1.61, 95% confidence interval 1.21 to 2.14), but the risk of coronary events did not differ significantly between the two groups. The lower risk of cardiovascular events in women with normal blood pressure compared with those with high normal blood pressure was consistent among all individual end points considered, although some of the secondary end points did not reach statistical significance in the fully adjusted models.

#### Blood pressure category and progression to hypertension

In total, 8686 (30.1%) of the 28 863 women without a diagnosis of hypertension at baseline developed incident hypertension during follow-up. Across the three baseline blood pressure categories, 8.2%, 22.7%, and 51.8% of women developed hypertension after five years of follow-up. The corresponding 10 year cumulative risks of incident hypertension were 14.8%, 34.0%, and 64.2%.

#### Blood pressure progression and cardiovascular events

During the first 48 months of follow-up, 22 886 (59.0%) women remained free of hypertension and 5694 (14.7%) progressed to hypertension—3274 (57.5%) women with baseline blood pressure below 130/85 mm Hg and 2420 (42.5%) women with high normal blood pressure at baseline. Women who progressed to hypertension had a higher event rate during

**Table 1** | Cox proportional hazards models to compare risk of first cardiovascular event according to baseline blood pressure category. Values are hazard ratios (95% confidence intervals)

End point	Baseline blood pressure, systolic/diastolic (mm Hg)			
	<120/75	120-9/75-84	130-9/85-9*	Hypertension†
<b>Major cardiovascular event‡</b>				
Crude	0.33 (0.26 to 0.42)	0.48 (0.39 to 0.60)	1.0	1.56 (1.30 to 1.86)
Age adjusted	0.44 (0.35 to 0.55)	0.56 (0.45 to 0.70)	1.0	1.41 (1.18 to 1.69)
Multivariable adjusted§	0.51 (0.40 to 0.64)	0.61 (0.48 to 0.76)	1.0	1.30 (1.08 to 1.57)
<b>Stroke</b>				
Crude	0.49 (0.36 to 0.69)	0.59 (0.43 to 0.82)	1.0	1.92 (1.46 to 2.53)
Age adjusted	0.66 (0.47 to 0.92)	0.69 (0.50 to 0.96)	1.0	1.74 (1.32 to 2.29)
Multivariable adjusted§	0.72 (0.51 to 1.01)	0.74 (0.53 to 1.03)	1.0	1.61 (1.21 to 2.14)
<b>Myocardial infarction</b>				
Crude	0.21 (0.15 to 0.31)	0.40 (0.29 to 0.55)	1.0	1.25 (0.96 to 1.62)
Age adjusted	0.27 (0.19 to 0.40)	0.45 (0.33 to 0.63)	1.0	1.15 (0.88 to 1.50)
Multivariable adjusted§	0.34 (0.23 to 0.50)	0.50 (0.36 to 0.71)	1.0	1.03 (0.78 to 1.35)
<b>Death from cardiovascular causes</b>				
Crude	0.37 (0.23 to 0.61)	0.51 (0.32 to 0.81)	1.0	2.10 (1.43 to 3.08)
Age adjusted	0.55 (0.33 to 0.91)	0.63 (0.39 to 1.01)	1.0	1.83 (1.25 to 2.69)
Multivariable adjusted§	0.66 (0.39 to 1.10)	0.65 (0.39 to 1.06)	1.0	1.68 (1.13 to 2.50)
<b>Coronary revascularisation</b>				
Crude	0.26 (0.20 to 0.34)	0.38 (0.30 to 0.49)	1.0	1.35 (1.12 to 1.64)
Age adjusted	0.31 (0.24 to 0.41)	0.42 (0.33 to 0.54)	1.0	1.26 (1.04 to 1.53)
Multivariable adjusted§	0.38 (0.29 to 0.50)	0.49 (0.38 to 0.64)	1.0	1.08 (0.88 to 1.32)
<b>Death from any cause</b>				
Crude	0.58 (0.47 to 0.71)	0.70 (0.57 to 0.85)	1.0	1.43 (1.19 to 1.72)
Age adjusted	0.81 (0.66 to 1.00)	0.84 (0.69 to 1.03)	1.0	1.27 (1.06 to 1.53)
Multivariable adjusted§	0.91 (0.73 to 1.13)	0.89 (0.72 to 1.10)	1.0	1.26 (1.04 to 1.52)

\*Reference category.

†Defined as previous diagnosis of hypertension, systolic blood pressure  $\geq 140$  mm Hg, diastolic blood pressure  $\geq 90$  mm Hg, or receiving blood pressure lowering treatment.

‡Defined as myocardial infarction, stroke, or death from cardiovascular causes.

§Adjusted for age, smoking, diabetes, history of hypercholesterolaemia, body mass index, exercise, alcohol consumption, highest educational level, and randomised treatment assignments (aspirin, vitamin E, and  $\beta$  carotene); owing to missing covariates, the multivariable (crude) analysis was based on 930 (982) major cardiovascular events, 456 (478) strokes, 365 (389) myocardial infarctions, 226 (239) cardiovascular deaths, 706 (748) revascularisations, and 1025 (1077) all cause deaths among 37 787 (39 322) women.

follow-up than women who remained free of hypertension and a lower event rate than women with hypertension at baseline (table 2). This difference between women with incident hypertension and baseline hypertension was substantially attenuated after multivariable adjustment, but having hypertension at baseline remained associated with a significant 39% increase in risk. After multivariable adjustment, women without progression to hypertension during the first 48 months had a 36% lower risk than women who progressed to hypertension.

In the second model, we found that women who had high normal blood pressure at baseline and who progressed to hypertension during follow-up had a similar risk of a major cardiovascular event to women with hypertension at baseline ( $P=0.28$ ). Women who had a lower blood pressure at baseline and who progressed to hypertension had a 30% lower risk of a cardiovascular event than women with high normal blood pressure at baseline, a difference that was of borderline statistical significance ( $P=0.07$ ).

## DISCUSSION

This study provides evidence that women's risk of having a major cardiovascular event is lower at lower

blood pressure, without evidence of a threshold level. Our findings are in line with previous reports from two different cohort studies and from a large meta-analysis.<sup>127</sup> The risk of women with high normal blood pressure having a major cardiovascular event was 64% higher compared with women with normal blood pressure and almost doubled compared with women with optimal blood pressure at baseline.

By combining the two categories normal and high normal blood pressure, the Joint National Committee 7 guidelines created a new blood pressure category called "prehypertension."<sup>6</sup> Because of the large differences in cardiovascular risk, separate consideration of these two groups may be reasonable. By maintaining two different blood pressure categories (normal and high normal blood pressure), the European guidelines for the management of hypertension may more accurately reflect the risk distribution among people with blood pressure levels below 140/90 mm Hg.<sup>5</sup>

Other findings further underscore substantial differences between these two groups. Among participants of the Framingham Study aged below 65, the risk of developing hypertension over a period of four years was 18% in those with normal blood pressure and

**Table 2** | Cox proportional hazards models to assess risk of first major cardiovascular event among women with incident diagnosis of hypertension during first 48 months of follow-up (n=38 787)

	Hazard ratio (95% confidence interval)			P trend	
	No progression* (n=22 886)	Progression to hypertension* (n=5694)	Baseline hypertension* (n=10 207)		
<b>First model</b>					
Events/person years	214/137 767	106/34 038	332/60 250		
Crude	0.50 (0.40 to 0.63)	1.0†	1.77 (1.42 to 2.20)	<0.0001	
Age adjusted‡	0.60 (0.48 to 0.76)	1.0†	1.51 (1.22 to 1.89)	<0.0001	
Multivariable adjusted§	0.64 (0.50 to 0.81)	1.0†	1.39 (1.11 to 1.74)	<0.0001	
<b>Second model</b>					
		(From below high normal)¶	(From high normal)¶		
Events/person years	214/137 767	47/19 622	59/14 416	332/60 250	
Crude	0.38 (0.29 to 0.51)	0.59 (0.40 to 0.86)	1.0†	1.35 (1.02 to 1.78)	<0.0001
Age adjusted‡	0.50 (0.37 to 0.66)	0.68 (0.46 to 1.00)	1.0†	1.25 (0.95 to 1.65)	<0.0001
Multivariable adjusted§	0.53 (0.40 to 0.72)	0.70 (0.47 to 1.03)	1.0†	1.17 (0.88 to 1.55)	<0.0001

\*No progression defined as a blood pressure <140/90 mm Hg at baseline and during at least 48 months of follow-up in absence of blood pressure lowering treatment; progression to hypertension defined as blood pressure <140/90 mm Hg without blood pressure lowering treatment at baseline and developing hypertension during first 48 months of follow-up; hypertension defined as previous diagnosis of hypertension, systolic blood pressure  $\geq$ 140 mm Hg, diastolic blood pressure  $\geq$ 90 mm Hg, or receiving blood pressure lowering treatment at baseline.

†Reference category.

‡Age at 48 months of follow-up used for adjustment.

§Adjusted for age, smoking, diabetes, body mass index, and alcohol consumption at 48 months and for baseline history of hypercholesterolaemia, exercise, highest educational level, and randomised treatment assignments (aspirin, vitamin E, and  $\beta$  carotene); owing to missing covariates, the multivariable analysis was based on 625 (compared with 652 in the crude and age adjusted analyses) major cardiovascular events during follow-up among 37 653 women.

¶Group of women with progression to hypertension divided into 3274 women who had a baseline blood pressure <130/85 mm Hg (below high normal) and 2420 who had baseline blood pressure 130-9/85-9 mm Hg (high normal).

37% in those with high normal blood pressure.<sup>3</sup> Our study confirms and expands these findings. Our study also indicates that women who progress to hypertension need to be identified early. Women who developed hypertension during the first 48 months of follow-up had a 56% increased risk of a major cardiovascular event in the last six years of follow-up compared with women who did not develop hypertension during at least four years.

Preventive and research efforts to reverse blood pressure progression and reduce cardiovascular events should be focused on people with high normal blood pressure. Physical exercise effectively reduces blood pressure levels independent of baseline blood pressure.<sup>8</sup> Dietary intervention was effective in reducing systolic blood pressure by 3.5 mm Hg and diastolic blood pressure by 2.1 mm Hg.<sup>9,10</sup>

Because women with high normal blood pressure also have an increased prevalence of diabetes and hypercholesterolaemia, a multidimensional intervention programme targeting all cardiovascular risk factors and including dietary modification and regular physical exercise should be the most efficient approach to reduce cardiovascular risk.<sup>11-14</sup>

Whether drug treatment should be used in people with high normal blood pressure is highly controversial.<sup>15</sup> No trial to date has examined the potential benefit of drug treatment to improve cardiovascular outcome in this large group of people. Thus, without hard end point data, blood pressure lowering drugs cannot be recommended.

#### Strengths and limitations

Strengths of this study are the large sample size, the prospective design, and the complete long term

follow-up with a large number of events. The study included predominantly white women, and our findings may not be generalisable to other populations. Another possible limitation is the use of self reported blood pressure and hypertension status. However, the prognostic value of self reported blood pressure in cohort studies involving US health professionals is similar to that of directly measured blood pressure in participants of other cohort studies.<sup>1</sup> Systolic blood pressure is the strongest cardiovascular risk factor after age in the women's health study,<sup>16</sup> further underscoring its predictive validity.

#### Conclusions

Women with high normal blood pressure have a substantially increased risk of developing hypertension or a major cardiovascular event compared with women with normal blood pressure. These people need close follow-up and lifestyle modifications. The increase in risk is substantially more pronounced in women with high normal blood pressure. Therefore, a classification using two different categories for people with "prehypertension" may be more accurate. Once hypertension has developed, the cardiovascular event rate is increased shortly after the diagnosis of hypertension has been made, especially among women with high normal blood pressure at baseline.

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## WHAT IS ALREADY KNOWN ON THIS TOPIC

Observational studies have shown a direct association between cardiovascular risk and blood pressure across a broad spectrum of blood pressure levels  
 Guidelines use different classification schemes for blood pressure levels currently considered as normal (prehypertension versus normal and high normal blood pressure)  
 Cardiovascular outcomes among people who progress to hypertension are not well defined

## WHAT THIS STUDY ADDS

Compared with women with normal blood pressure, those with high normal blood pressure have a substantially higher risk of cardiovascular events and incident hypertension  
 Maintaining two different blood pressure categories for people with prehypertension seems to be appropriate  
 Risk of cardiovascular events among women who progress to hypertension is increased shortly after a diagnosis of hypertension has been made

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**Competing interests:** None declared.

**Ethical approval:** Institutional review board of Brigham and Women's Hospital, Boston.

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## Acupuncture as an adjunct to exercise based physiotherapy for osteoarthritis of the knee: randomised controlled trial

Nadine E Foster,<sup>1</sup> Elaine Thomas,<sup>1</sup> Panos Barlas,<sup>2</sup> Jonathan C Hill,<sup>1</sup> Julie Young,<sup>1</sup> Elizabeth Mason,<sup>1</sup> Elaine M Hay<sup>1</sup>

<sup>1</sup>Primary Care Musculoskeletal Research Centre, Keele University, Stafford ST5 5BG

<sup>2</sup>School of Health and Rehabilitation, Keele University

Correspondence to: N E Foster n.foster@keele.ac.uk

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### ABSTRACT

**Objective** To investigate the benefit of adding acupuncture to a course of advice and exercise delivered by physiotherapists for pain reduction in patients with osteoarthritis of the knee.

**Design** Multicentre, randomised controlled trial.

**Setting** 37 physiotherapy centres accepting primary care patients referred from general practitioners in the Midlands, United Kingdom.

**Participants** 352 adults aged 50 or more with a clinical diagnosis of knee osteoarthritis.

**Interventions** Advice and exercise (n=116), advice and exercise plus true acupuncture (n=117), and advice and exercise plus non-penetrating acupuncture (n=119).

**Main outcome measures** The primary outcome was change in scores on the Western Ontario and McMaster Universities osteoarthritis index pain subscale at six

months. Secondary outcomes included function, pain intensity, and unpleasantness of pain at two weeks, six weeks, six months, and 12 months.

**Results** Follow-up rate at six months was 94%. The mean (SD) baseline pain score was 9.2 (3.8). At six months mean reductions in pain were 2.28 (3.8) for advice and exercise, 2.32 (3.6) for advice and exercise plus true acupuncture, and 2.53 (4.2) for advice and exercise plus non-penetrating acupuncture. Mean differences in change scores between advice and exercise alone and each acupuncture group were 0.08 (95% confidence interval -1.0 to 0.9) for advice and exercise plus true acupuncture and 0.25 (-0.8 to 1.3) for advice and exercise plus non-penetrating acupuncture. Similar non-significant differences were seen at other follow-up points. Compared with advice and exercise alone there were small, statistically significant improvements in pain