Review

Is It Time to Treat Prehypertension?

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Prehypertension, defined as blood pressure between 120–139/80–89 mmHg, is a major public health concern. The condition is very prevalent (30% of the adult population), is often associated with other cardiovascular risk factors and independently increases the risk of hypertension and subsequent cardiovascular events. The mechanism of elevated risk for cardiovascular events associated with prehypertension is presumed to be the same as that of hypertension. In the general population, prehypertension can be lowered by lifestyle modifications, but often not reliably. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) recommendation for prehypertension management with optimal weight control (largely through diet and exercise) remains the mainstay, except for individuals with diabetes, chronic kidney disease, and perhaps known coronary artery disease, because of the shot-term cost considerations and unproven long-term prognosis. The recently published Trial of Preventing Hypertension (TROPHY) is the first study of pharmacologic intervention among those with prehypertension. Results from this trial demonstrated that angiotensin receptor blockade (ARB) retards age-related blood pressure increases in prehypertensive patients. In this review, we discuss the options for pharmacologic intervention of prehypertension, with a focus on the TROPHY trial results. (*Hypertens Res* 2008; 31: 1681–1686)

***Key Words*: angiotensin receptor blocker, candesartan, hypertension, prehypertension, Trial of Preventing Hypertension (TROPHY) study**

Introduction

In 2003, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) introduced "prehypertension" as a category in blood pressure (BP) classification. Prehypertension is defined as systolic blood pressure (SBP) of 120–139 mmHg or diastolic blood pressure (DBP) of 80–89 mmHg (Table 1). This was prompted by the observation from meta-analyses showing a continuous relationship between BP and cardiovascular risk (*1*, *2*).

A report from the Tecumseh Blood Pressure study several years ago found that participants with "borderline BP," or "high normal BP" (as it was termed previously), had more cardiovascular risk factors than those with normal BP in a healthy population. Also, participants with high normal BP were more likely than normotensives to have an elevated risk of fatal or non fatal cardiovascular events (*3*–*6*).

Despite the new nomenclature, the treatment recommendations remain limited to nonpharmacologic treatment alone. While non-pharmacologic methods are successful experimentally, implementation into clinical settings is fraught with difficulty. The new challenge is to investigate and properly implement pharmacologic treatment into the treatment paradigm. In this review, the most recent data regarding pharmacological treatment options for prehypertension will be discussed.

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Table 1. JNC-7 Classification Blood Pressure

	SBP (mmHg)	DBP (mmHg)
Normal	<120	<80
Prehypertension	120–139	80–89
Stage 1	140–159	90–99
Stage 2	>160	>100

JNC-7, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Epidemiology and Target Organ Damage

The prevalence of prehypertension in the United States from the 1999 to 2000 National Health And Nutrition Survey (NHANES) data was ≈70 million in people aged ≥20 years. Surprisingly, many more men (42 million) than women (28 million) had prehypertension (*7*, *8*). The prevalence of prehypertension in blacks seemed roughly similar to that in whites. Among younger adults (20–39 years old), African Americans had the highest prevalence at 37.4% compared with whites and Mexican Americans, at 32.2 and 30.9%, respectively. However, in adults aged 40–59 years old and 60 years or older, the pattern was reversed, with a higher prevalence of prehypertension in whites and Mexican Americans than African Americans. The age-adjusted prevalence of prehypertension was greater in men than in women, with values of 39.0 *vs*. 23.1%, respectively. The risk of developing hypertension was approximately 90% for prehypertensive individuals who live to be 75 years old in the USA (*9*).

Abnormalities in other cardiovascular disease (CVD) risk factors are more common in prehypertensive than normotensive individuals. A study of the 1999 to 2000 NHANES data suggested that 64% of prehypertensive subjects had ≥1 other abnormal CVD risk factors (*7*); the percentage increased to 94% in those ≥60 years of age. In a separate investigation, 93% of prehypertensive subjects were reported to have ≥1 other CVD risk factor abnormalities (*10*). With respect to specific risk factors, the risk ratios for obesity, dyslipidemia, insulin resistance, metabolic syndrome, and diabetes were all greater in prehypertensive than in normotensive subjects and were intermediate between those found for subjects with normotension and for subjects with hypertension (*11–14*).

Also, microalbuminuria is more common in prehypertension than normotension (*15*), as are abnormalities in circulating inflammatory markers for atherosclerotic disease such as C-reactive proteins, interleukin 6, and tumor necrosis factor-α (*16–18*). Toikka *et al*. demonstrated that prehypertension was associated with increased carotid and brachial intima-media thickness (*19*), while Washio *et al*. demonstrated that there was an increased risk of carotid stenosis in patients with prehypertension (*20*).

Using transthoracic echocardiography, Erdogan *et al*. evaluated left ventricular (LV) diastolic function and aortic elastic properties in 60 subjects with prehypertension, 70 patients with hypertension and 50 normotensive healthy volunteers. None of the subjects had any systemic disease. LV diastolic function was more significantly impaired in the hypertension group than in the prehypertension group or in the control group, but it was not significantly different between the prehypertension and control group. Aortic distensibility was significantly lower, and aortic stiffness index was significantly higher in both the hypertension and the prehypertension groups than in the control group. However, aortic elastic properties did not differ significantly between the prehypertension and hypertension groups (*21*).

Prehypertension was associated with an increased incidence of CVD, particularly at SBP levels of 130 to 139 mmHg and DBP levels in the 85 to 89 mmHg range (*4*, *22*), as seen with diabetes or glucose intolerance (*14*, *23*, *24*). In a study of 11,116 subjects followed for ≈10 years, prehypertensive persons demonstrated a significant increase in the incidence of myocardial infarction, but not of stroke compared with normotensive subjects (*25*). In a separate investigation, mortality from CVD was significantly greater in prehypertensive than in normotensive individuals, but the differences were not present when adjustments were made for other CVD risk factors (*10*).

Data from the Framingham Heart Study have shown that prehypertension increased the risk of myocardial infarction by 3.5-fold and coronary artery disease by 1.7-fold. This risk was lower than that with hypertension, as expected. When analyzed separately by sex, an even higher risk of myocardial infarction (4.2-fold) and coronary artery disease (3.4-fold) was seen in men. No relationship between prehypertension and risk of stroke was observed. It is possible that such a relationship was missed because of the smaller number of stroke events in the cohort. Among patients with prehypertension, the risk of coronary artery disease was elevated 2.9-fold in persons aged 45 to 64 years and elevated 4.4-fold in persons 65 years or older compared with persons younger than 45 years. Risks were also higher in men (by 2.5 times), persons with diabetes mellitus (by 2.1 times), and patients with hypercholesterolemia (by 1.5 times). Body mass index and smoking status did not influence the risk of coronary artery disease in prehypertensive patients (*24*).

In the randomised, double-blind trial—the EUropean trial on Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease (EUROPA)—12,218 patients with stable CAD and without heart failure were randomized to once-daily perindopril 8 mg or to placebo. After a mean follow-up of 4.2 years, a significant ($p=0.0003$) relative risk reduction (RRR) of 19.9% for the primary endpoint (cardiovascular death, non-fatal myocardial infarction [MI] and resuscitated cardiac arrest) occurred with perindopril *vs*. placebo among patients with SBP<140 mmHg and DBP<90 mmHg (*25*).

Table 2. Lifestyle Modifications Recommended in JNC-7 for the Treatment of Prehypertension

1. Maintain body mass index between 18.5 and 24.9 kg/m^2; this is expected to reduce SBP by 5 to 20 mmHg for each 10-kg reduction in weight
2. Consume a diet rich in fruits and vegetables, as well as low-fat dairy products; this is expected to reduce SBP by 8 to 14 mmHg
3. Restrict sodium to no more than 6 g of table salt per day; this is expected to reduce SBP by 2 to 8 mmHg
4. Walk briskly at least 30 min per day or engage in other regular aerobic physical activity; this is expected to reduce SBP by 4 to 9 mmHg
5. Use alcohol in moderation; this reduces SBP by 2 to 4 mmHg

JNC-7, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; SBP, systolic blood pressure.

In the randomized, double-blind PROGRESS study composed of 6,105 patients with a previous history of stroke or transient ischaemic attack, the risk of stroke was 10% in recipients of perindopril±indapamide and 14% in recipients without indapamide (RRR 27%; $p<0.0001$) over a mean follow-up of 3.9 years in patients with SBP<160 mmHg. BP was reduced by 9 mmHg SBP and 4 mmHg DBP in recipients of perindopril±indapamide compared with those receiving placebo. Perindopril±indapamide reduced the risk of nonfatal myocardial infarction by 38% (95% confidence interval [CI] 14–55) and congestive heart failure by 26% ($p=0.02$) (*26*).

The Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) trial was designed to assess the effects on vascular disease of such an approach using a fixed combination of the angiotensin converting enzyme (ACE) inhibitor, perindopril, and the diuretic, indapamide, in a diverse population of patients with type 2 diabetes and a broad range of BP values. After a mean of 4.3 years of follow-up, 73% of those assigned active treatment and 74% of those assigned control remained on randomized treatment. Compared with patients assigned placebo, those assigned the active therapy had a mean reduction in SBP of 5.6 mmHg and DBP of 2.2 mmHg. The risk of a major macrovascular or microvascular event was reduced by 10% (861 [15.5%] active *vs*. 938 [16.8%] placebo; hazard ratio 0.91, 95% CI 0.83–1.00, $p=0.04$) in patients with SBP/DBP<140/90 mmHg (*27*).

Finally, data coming from Japan suggest that subjects with high-normal BP (from 130/85 to 139/89 mmHg) at health checkup (checkup-BP≥130/85 mmHg) might already experience workplace hypertension. Job strain is a risk factor for hypertension, particularly in hard-working men. Some people have been reported to have higher BP at work than in the clinic. Job strain causes an increase in ambulatory BP (ABP) at work, at home, and during sleep. A previous study reported that ABP was higher than clinic BP in normotensive subjects, whereas the reverse was typically true in hypertensives (*28–32*).

Treatment of Prehypertension

Non-Pharmacological Treatment

How best to manage prehypertension has been the subject of recent debate. Several studies have demonstrated the efficacy of dietary approaches, alone or in combination with other lifestyle modifications, to reduce BP in both prehypertensive and hypertensive persons. The Dietary Approaches to Stop Hypertension (DASH) eating plan, which uses a diet rich in fruits, vegetables, legumes, nuts, and low-fat dietary products and low in saturated fats, induced a significant lowering of BP, which was reduced even further when dietary sodium was restricted. In the Optimal Macro-Nutrient Intake (OMNI) Heart Study, in which the DASH diet was modified to provide more protein and unsaturated fat and less carbohydrate, impressive reductions of BP were also achieved. The PREMIER trial studied the combined effects of diet, physical activity, and weight reduction in 3 groups of prehypertensive and hypertensive subjects over an 18-month period. Although all 3 of the groups demonstrated significant reductions in BP in both prehypertensive and hypertensive subjects, the amount of decrease in the group given relatively minimal counselling was both surprising and gratifying in view of the previous difficulties with obtaining long-term behavioural changes to improve the cardiovascular risk status (*33–36*).

The JNC-7 report has recommended the adoption of healthy lifestyles to achieve BP goals except in prehypertensive subjects with diabetes or chronic renal disease in whom drug treatment is also advocated. In particular, maintaining a body mass index between 18.5 and 24.9 kg/m^2 is expected to reduce SBP by 5 to 20 mmHg for each 10-kg reduction in weight (*2*). Consuming a diet rich in fruits and vegetables, as well as low-fat dairy products is expected to reduce SBP by 8 to 14 mmHg. Restricting sodium to no more than 6 g of table salt per day is expected to reduce SBP by 2 to 8 mmHg. Walking briskly at least 30 min per day or engaging in other regular aerobic physical activity is expected to reduce SBP by 4 to 9 mmHg. Using alcohol in moderation reduces SBP by 2 to 4 mmHg (*1*) (Table 2).

Pharmacological Treatment

The Trial of Preventing Hypertension (TROPHY) study was an investigator-initiated trial to examine whether early pharmacological treatment in subjects with "high-normal" BP might prevent or delay the development of clinical hypertension. This was a 4-year, multicenter, randomized, double-blind study in untreated subjects aged 30 to 65 years with entry BPs of 130 to 139/≤89 mmHg or ≤139/85 to 89 mmHg. They evaluated 809 subjects (59% males, average age 49.0±8.1 years) in 71 study centers in the USA. A total of 409 participants were randomly assigned to a fixed (16 mg once daily) dose of candesartan cilexetil, and 400 to placebo. After 2 years, the candesartan group was switched to placebo, and the placebo group continued taking placebo. Data from 772 participants (391 in the candesartan group and 381 in the placebo group; mean age, 48.5 years; 59.6% men) were available for analysis. The entry BP was 134±4.3/84.8±3.9 mmHg. The participants of the TROPHY study with high normal BP exhibited additional cardiovascular risk factors. Of the subjects, 96% had at least one, 81% had two or more, and 13% had five or more additional risk factors. When a participant reached the study end point of stage 1 hypertension, treatment with antihypertensive agents was initiated. Both the candesartan group and the placebo group were instructed to make changes in lifestyle to reduce BP throughout the trial. The main outcome measure was the development of clinical (treatment-requiring) hypertension assessed by an automated (blinded) BP measurement device (*37*, *38*). During the first 2 years, hypertension developed in 154 participants in the placebo group and 53 of those in the candesartan group (8% absolute and a 66.3% relative risk reduction; $p<0.0001$). Using the absolute difference between groups, one can calculate that four people with prehypertension need to be treated to prevent one case of hypertension in 2 years. After 4 years, hypertension had developed in 240 participants in the placebo group and 208 of those in the candesartan group (9.8% absolute and 15.6% relative risk reduction; $p<0.007$). The treatment was well-tolerated. The study dropout rate was 14.8% (120 subjects). Serious adverse events occurred in 3.5% of the participants assigned to candesartan and 5.9% of those receiving placebo (*39*, *40*).

Also, 2 years after discontinuing candesartan, there was a significant reduction of hypertension in the group previously treated with candesartan. The proportion of hypertension-free cases was 26.5% greater in the candesartan group. The median hypertension-free time was 1.1 years longer in the candesartan group. After stopping the treatment, this difference narrowed, but still, at the end of 4 years (2 years after stopping antihypertensive medication), there was a relative risk reduction of 13.6% and an absolute risk reduction of 9.8%. The time to development of hypertension was 2.2 years in the untreated and 3.3 years in the treated group. These results demonstrate that hypertension may be prevented or delayed by treatment of prehypertension using antihypertensive medication (*41*, *42*).

In addition, the results from the TROPHY study suggest that the renin-angiotensin system plays a critical role in the development of early hypertension and pre-hypertension, although it is still possible that similar results to those reported in the TROPHY study can be obtained using other antihypertensive agents such as CCBs or β-blockers. However, such studies have yet to be designed and carried out.

Conclusions

Among an estimated 65 million people in the USA. with prehypertension, approximately 25 million have BP at levels comparable to those of the TROPHY participants. Almost 16 million will become hypertensive over the next 4 years based on the experience of the TROPHY placebo group. A successful intervention in such a large population could therefore have a major public health impact. The recommended lifestyle measures for BP control in prehypertension had no demonstrable effect on public health. If non-occurrence of hypertension during the active treatment is considered the goal, then success was achieved in 86.4% of the candesartan group. TROPHY also suggested that the effect of active treatment in delaying hypertension can extend up to 2 years after discontinuing treatment.

Another factor that needs to be considered is the issue of cost effectiveness in treating prehypertension. A head-to-head comparison of the cost effectiveness of lifestyle modification and pharmacological treatment of prehypertension would therefore be of great interest. Due to the costs and risks of treatment, new trials should be planned to demonstrate a conclusive reduction in cardiovascular events by early administration of antihypertensive medication. In the interim period, lifestyle modifications for BP control, elimination of risk factors, and close monitoring of BP are recommended.

References

1. Chobanian AV, Bakris GL, Black HR, *et al*: Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute. *Hypertension* 2003; **42**: 1206–1252.
2. Prospective Studies Collaboration: Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; **360**: 1903–1913.
3. Julius S, Jamerson K, Mejia A, *et al*: The association of borderline hypertension with target organ changes and higher coronary risk: Tecumseh Blood Pressure Study. *JAMA* 1990; **264**: 354–358.
4. Vasan RS, Larson MG, Leip EP, *et al*: Impact of high-normal blood pressure on the risk of cardiovascular disease. *N Engl J Med* 2001; **345**: 1291–1297.
5. Neaton JD, Kuller L, Stamler J, Wentworth DN: Impact of systolic and diastolic blood pressure on cardiovascular mortality. in Laragh JH, Brenner BM (eds): Hypertension:

Pathophysiology, Diagnosis, and Management, 2nd ed. New York, Raven Press, 1995, pp 127–144.
6. Lowe LP, Greenland P, Ruth KJ, Dyer AR, Stamler R, Stamler J: Impact of major cardiovascular disease risk factors, particularly in combination, on 22-year mortality in women and men. *Arch Intern Med* 1998; **158**: 2007–2014.
7. Greenlund KJ, Croft JB, Mensah GA: Prevalence of heart disease and stroke risk factors in persons with prehypertension in the United States, 1999–2000. *Arch Int Med* 2004; **164**: 2113–2118.
8. Chobanian AV: Prehypertension revisited. *Hypertension* 2006; **48**: 812–814.
9. Vasan RS, Beiser A, Seshadri S, *et al*: Residual lifetime risk for developing hypertension in middle-aged women and men: the Framingham Heart Study. *JAMA* 2002; **287**: 1003–1010.
10. Mainous AG, Everett CJ, Liszka H, King DE, Egan BM: Prehypertension and mortality in a nationally representative cohort. *Am J Cardiol* 2004; **94**: 1496–1500.
11. Okosun IS, Boltri JM, Anochie LK, Chandra KMD: Racial/ethnic differences in prehypertension in American adults: population and relative attributable risk of abdominal obesity. *J Hum Hypertens* 2004; **18**: 849–855.
12. Tsai P-S, Ke T-L, Huang C-J, *et al*: Prevalence and determinants of prehypertension status in the Taiwanese general population. *J Hypertens* 2005; **223**: 1355–1360.
13. Cordero A, Laclaustra M, Leon M, *et al*: Prehypertension is associated with insulin resistance state and not with an initial renal function impairment. *Am J Hypertens* 2006; **19**: 189–196.
14. Zhang Y, Lee ET, Devereux RB, *et al*: Prehypertension, diabetes, and cardiovascular disease risk in a population-based sample: the Strong Heart Study. *Hypertension* 2006; **47**: 410–414.
15. Lee JE, Kim Y-G, Choi Y-H, Huh W, Kim DJ, Oh HY: Serum uric acid is associated with microalbuminuria in prehypertension. *Hypertension* 2006; **47**: 962–967.
16. King DE, Egan BM, Mainous AG, Geesey ME: Elevation of C-reactive protein in people with prehypertension. *J Clin Hypertens* 2004; **6**: 562–568.
17. Chrysohoou C, Pitsavos C, Panagiotakos DB, Skoumas J, Stefanadis C: Association between prehypertension status and inflammatory markers related to atherosclerotic disease. The ATTICA Study. *Am J Hypertens* 2004; **17**: 568–573.
18. Papadopoulos DP, Makris TK, Krespi PG, *et al*: Adiponectin and resistin plasma levels in healthy individuals with prehypertension. *J Clin Hypertens* 2005; **7**: 729–733.
19. Toikka JO, Laine H, Ahotupa M, *et al*: Increased arterial intima-media thickness and *in vivo* LDL oxidation in young men with borderline hypertension. *Hypertension* 2000; **36**: 929–933.
20. Washio M, Tokunaga S, Yoshimasu K, *et al*: Role of prehypertension in the development of coronary atherosclerosis in Japan. *J Epidemiol* 2004; **14**: 57–62.
21. Erdogan D, Caliskan M, Yildirim I, *et al*: Effects of normal blood pressure, prehypertension and hypertension on left ventricular diastolic function and aortic elastic properties. *Blood Press* 2007; **16**: 114–121.
22. Liszka HA, Mainous AG, King DE, Everett CJ, Egan BM: Prehypertension and cardiovascular morbidity. *Ann Fam Med* 2005; **3**: 294–299.
23. Kshirsagar AV, Carpenter M, Bang H, Wyatt SB, Colindres RE: Blood pressure usually considered normal is associated with an elevated risk of cardiovascular disease. *Am J Med* 2006; **199**: 133–141.
24. Qureshi AI, Suri FK, Kirmani JF, Divani AA, Mohammed Y: Is prehypertension a risk factor for cardiovascular diseases? *Stroke* 2005; **36**: 1859–1863.
25. Fox KM, European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease Investigators: Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003; **362**: 782–788.
26. PROGRESS Collaborative Group: Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001; **358**: 1033–1041.
27. Patel A, MacMahon S, Chalmers J, *et al*: Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet* 2007; **370**: 829–840.
28. Harada K, Karube Y, Saruhara H, Takeda K, Kuwajima I: Workplace hypertension is associated with obesity and family history of hypertension. *Hypertens Res* 2006; **29**: 969–976.
29. Light KC, Turner JR, Hinderliter AL: Job strain and ambulatory work blood pressure in healthy young men and women. *Hypertension* 1992; **20**: 214–218.
30. Fiedler N, Favata E, Goldstein BD, Gochfeld M: Utility of occupational blood pressure screening for the detection of potential hypertension. *J Occup Med* 1988; **30**: 943–948.
31. Schnall PL, Schwartz JE, Landsbergis PA, Warren K, Pickering TG: Relation between job strain, alcoholic, and ambulatory blood pressure. *Hypertension* 1992; **19**: 488–494.
32. James GD, Pickering TG, Yee LS, Harshfield GA, Riva S, Laragh JH: The reproducibility of average ambulatory, home, and clinic pressures. *Hypertension* 1988; **11**: 545–549.
33. Sacks FM, Svetkey LP, Vollmer WM, *et al*, DASH–Sodium Collaborative Research Group: Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. *N Engl J Med* 2001; **344**: 3–10.
34. Appel LJ, Sacks FM, Carey VJ, *et al*, OmniHeart Collaborative Research Group: Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: results of the OmniHeart randomized trial. *JAMA* 2005; **294**: 2455–2464.
35. Appel LJ, Champagne CM, Harsha DW, *et al*, Writing Group of the PREMIER Collaborative Research Group: Effects of comprehensive lifestyle modification on blood pressure control: main results of the PREMIER clinical trial. *JAMA* 2003; **289**: 2083–2209.
36. Elmer PJ, Obarzanek E, Vollmer WM, *et al*, PREMIER Collaborative Research Group: Effects of comprehensive lifestyle modification on diet, weight, physical fitness, and blood pressure control: 18-month results of a randomized

trial. *Ann Int Med* 2006; **144**: 485–495.
37. Julius S, Nesbitt S, Egan B, *et al*, TROPHY Study Group: Trial of preventing hypertension: design and 2-year progress report. *Hypertension* 2004; **44**: 146–151.
38. Nesbitt SD, Julius S, Leonard D, Egan BM, Grozinski M: Is low-risk hypertension fact or fiction? Cardiovascular risk profile in the TROPHY study. *Am J Hypertens* 2005; **18**: 980–985.
39. Julius S, Nesbitt SD, Egan BM, *et al*: Feasibility of treating prehypertension with an angiotensin-receptor blocker. *N Engl J Med* 2006; **354**: 1685–1697.
40. Julius S: Should the results of TROPHY affect the JNC 7 definition of prehypertension? *Curr Hypertens Rep* 2007; **9**: 202–205.
41. Kjeldsen SE, Narkiewicz K, Hedner T: An American TROPHY in the prevention of hypertension. *Blood Press* 2006; **15**: 132–134.
42. Suri MF, Qureshi AI: Prehypertension as a risk factor for cardiovascular diseases. *J Cardiovasc Nurs* 2006; **21**: 478–484.