REVIEW ARTICLE

Benefits of antihypertensive drugs when blood pressure is below 140/90 mmHg

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KEY WORDS

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ABSTRACT

Antihypertensive medications are used to lower blood pressure (BP) but, ultimately, their true value lies in reductions in morbidity and mortality (cardiovascular, cerebrovascular, and renal diseases). Hypertension is defined discreetly (generally 140/90 mmHg) but the actual relationship between BP and adverse cardiac and cerebrovascular outcomes is continuous. Observational studies have demonstrated a powerful log-linear relationship between BP and mortality due to ischemic heart disease (IHD) or stroke over the range of 115/75 to 185/115 mmHg. Clinical trials and meta-analyses have clearly demonstrated benefits of antihypertensive drugs in nonhypertensive individuals: delay or prevention of the onset of hypertension and microalbuminuria and reduced morbidity and mortality from IHD, stroke, and chronic kidney disease. This is not surprising given that various antihypertensive drug classes have multiple potential beneficial effects. A persistent concern is that overtreatment of hypertension may increase risk in individuals with coronary artery disease, but a "J-curve" effect is not consistently found in clinical studies. The use of antihypertensive drugs in at-risk individuals who are below the traditional threshold (140/90 mmHg) is fully justifiable, but the decision requires adequate clinical experience and judgment and a full assessment of risks and benefits.

Introduction The most important breakthroughs in longevity and functionality for people with chronic cardiovascular diseases (CVD) are the drugs that control the major underlying risk factors for CVD, especially hypertension and dyslipidemia. The potential value of antihypertensive therapy in a given individual depends on persistence with therapy, the degree of blood pressure (BP) lowering, and certain intrinsic properties of the drugs themselves.[1] This review covers these core issues and focuses on the specific question of whether there are identifiable benefits of antihypertensive drugs in individuals whose BP values are consistently less than 140/90 mmHg (e.g., "nonhypertensive individuals").

How can antihypertensive drugs be beneficial at lower blood pressure levels? Answer: There are multiple effects of certain antihypertensive drug classes beyond their abilities to lower BP. Also, hypertension is a disease spectrum where different thresholds are needed for optimal management. The desired degree of BP lowering should be considered along with the comorbidities present in the individual patient.

Pleiotropic effects of drugs Many drugs have multiple biologic ("pleiotropic") effects, both beneficial and adverse, that can affect therapeutic outcomes. An example of a beneficial pleiotropic effect of dihydropyridine calcium channel blockers was the improved outcome of individuals at high risk for ischemic heart disease (IHD) in the ACCOMPLISH study (The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension).[2] In this study, BP was well controlled (about 131/74 mmHg in parallel groups that received one of 2 combinations: angiotensin-converting enzyme [ACE] inhibitor/hydrochlorothiazide or ACE inhibitor/amlodipine). Amlodipine reduced the composite CVD endpoint about 20% more than hydrochlorothiazide. The reason for this additional benefit is unknown but may simply reflect the anti-ischemic properties of amlodipine in a population designed by selection criteria to overweight clinical and subclinical IHD.[3] A more puzzling question is whether drugs that block the renin-angiotensin system (RAS) improve cardiovascular and renal outcomes more than other antihypertensive drug classes. RAS blockers

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are universally recommended for the treatment of heart failure or renal failure; yet it remains difficult to separate effects attributable to BP lowering from those representing additional mechanisms of action. In ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), thiazide-type diuretics (which activate the RAS) were found to be similar to ACE inhibitors in their respective abilities to protect against myocardial infarction (MI) and stroke.[4]

Age and blood pressure thresholds Age is related continuously to systolic BP (SBP) throughout life. In children, hypertension is defined as BP above the 95th percentile according to age, height, and sex.[5] It is also well known among practitioners that young children develop signs and symptoms of hypertensive crisis at much lower levels than adults, sometimes below 140/90 mmHg. In adults, the age-SBP relationship persists into the ninth decade of life.[6] Overall, although logic might dictate that the diagnosis of hypertension should always be age-normalized, rigid thresholds are used, largely because of practical aspects related to consistency of diagnosis and monitoring.

Compelling indications There is a general consensus that there should be lower BP targets in individuals with "compelling indications".[7] A compelling indication is a high-risk condition associated with hypertension for which there is clinical trial evidence of a specific improvement in morbidity or mortality associated with a particular antihypertensive drug or drug class.[7] The Seventh Report of the Joint National Committee (JNC7) identified several such conditions (post-MI, high-risk for coronary disease, heart failure, prior stroke, chronic kidney disease [CKD], and diabetes) and recommended specific therapies for these conditions such as ACE inhibitors or angiotensin-receptor blockers for hypertensive individuals with diabetes or CKD.[7] JNC7 also recommended that the appropriate BP target in diabetes and CKD is lower than the general population (<130/80 mmHg), based on observed clinical trial benefits. Subsequently, other major international guidelines have adopted a similar approach.[8,9] Because a large body of evidence demonstrates that individuals with hypertensive complications benefit from antihypertensive drugs (even when BP is <140/90 mmHg), by definition there is benefit attributable to antihypertensive drugs in nonhypertensive individuals. What is less clear is the degree to which the observed benefit of antihypertensive drugs can be attributed to the lower BP target vs. the specific characteristics of the drugs themselves.

How strongly are lower blood pressure and lower disease risk correlated in observational studies?

Answer: Hypertension is an extremely powerful predictor of cardiovascular, cerebrovascular, and renal diseases across the entire BP spectrum, including BP values below the arbitrary 140/90 mmHg cutoff that defines hypertension.

Ischemic heart disease The association of chronic hypertension (sustained BP >140/90 mmHg) with increased CVD event rates was first noted by the insurance industry and later more precisely documented in classic observational studies such as the Framingham Heart Study[10] and the Multiple Risk Factor Intervention Trial follow-up.[11] The false impression that hypertension is a discrete disease or "step function" arises from less rigorous studies such as InterHEART,[12] an international case-controlled study that underestimated the importance of BP in CVD risk. In addition to the general weakness of the case-control format that was used, there was significant imprecision introduced by the self-reporting of hypertension status and the varying definitions of hypertension in different countries, changes in these definitions over time, and additional physician-dependent interpretations. The CVD odds ratio attributable to hypertension was 1.91, while that published for apolipoprotein (Apo) B/ApoA1 ratio was 3.25, but the latter was derived from comparing the highest and lowest quintiles for the lipoproteins, a much more sensitive approach. Had the same technique been used for measured BP, it is likely that the odds ratio attributable to measured BP would have been much higher (stage 2 hypertension carries 8 times the CVD risk of normotension).

SBP is a more precise IHD risk predictor than diastolic BP (DBP),[11,13] but hypertension-attributable risk is powerful and continuous. In a world-wide meta-regression study, the Prospective Studies Collaboration[14] found an extremely precise log-linear relationship between "casual" (office) BP values and heart attack or stroke mortality in 61 studies in over 986,000 individuals aged ≥40 years who were followed for a mean of 12.7 years. For each 20 mmHg increase in SBP (or 10 mmHg DBP) over the range of 115 to 185 mmHg SBP (or 75 to 115 mmHg DBP), the risk of a fatal heart attack doubled.[14] This relationship has come to be called the "20/10 rule" and it is extremely useful for teaching health professionals and patients. The take-home message is clear: even if BP is below 140/90 mmHg, the higher the BP, the higher the CVD risk. Also, in theory, lowering SBP from 135 to 115 mmHg should reduce by half the number of fatal heart attacks or strokes in individuals with prehypertension.

The theoretical implications of the 20/10 rule for MI in the United States are shown in TABLE 1, which was derived from the world-wide meta-regression analysis[14] and the United States MI rate. In most populations, about half has normal BP (<120/80 mmHg), about 1/4 has prehypertension (120–139/60–89 mmHg), about 1/5 has stage 1 hypertension (140–159/90–99 mmHg), and 1/20 has stage 2 hypertension (≥160/100 mmHg).[7] Because of these differences in category prevalence, there are almost as many heart attacks in the US nonhypertensive population (normal + prehypertension = about 550,000 annually) as in the hypertensive population (stage 1 + stage 2 = about

TABLE 1 Hypothetical hypertension-attributable risk and corresponding risk-reduction for myocardial infarction in United States adults attributable to a 20 mmHg reduction in systolic blood pressure by JNC7 blood pressure stage

Category	Population at risk	Hypertension--attributable relative risk	MI rate per 10,000	MI per BP category	MI averted per year (SBP 20 mmHg lower)	NNT to prevent 1 MI per year
normal	112,500,000	1	2.5	281,000	140,500	800
prehypertension	56,250,000	2	5.0	281,000	140,500	400
stage 1 hypertension	45,000,000	4	10	450,000	225,000	200
stage 2 hypertension	11,250,000	8	20	225,000	112,500	100
total	225,000,000	–	5.5	1,237,000	618,500	364

Data are predicated on the population distribution of United States adults: normal BP (50%), prehypertension (25%), stage 1 hypertension (20%) and stage 2 hypertension (5%). Hypertension-attributable risk assumes the same log-linear relationship between SBP and that found in meta-regression studies.[14] NNT assumes that a 20 mmHg reduction in SBP will reduce MI risk by 50% in each category.

Abbreviations: BP – blood pressure, MI – myocardial infarction, NNT – number-needed-to-treat to avoid 1 event, SBP – systolic BP

670,000 annually) and almost as many MIs in the prehypertension category as in stage 1 hypertension. The most interesting aspect of this analysis, however, is the number-needed-to-treat (NNT) in each category to prevent a fatal MI (800 in normotensives and 100 in those with stage 2 hypertension). From a public health perspective, it is potentially justifiable to treat prehypertension but achieving a 50% risk reduction (decrease in SBP of 20 mmHg) requires treatment of 400 people to prevent 1 event annually.

Stroke and chronic kidney disease The Prospective Studies Collaboration also found a continuous relationship between BP and risk of fatal stroke that was very similar to that observed for fatal MI; risk was stronger for SBP and pulse pressure than for DBP.[14] As with MI and stroke, there is a very strong continuous relationship between BP and CKD progression and incidence, stronger for SBP than for DBP.[15] As with other forms of target organ damage, the optimum BP for patients with CKD has not been clearly established; the general consensus is that BP should be <130/80.[7]

Is lower blood pressure better in clinical trials?

Answer: "Lower is better" for preventing hypertension, albuminuria, stroke, and end-stage renal disease; the picture is less clear for individuals with known IHD.

Prevention or delay of hypertension An important principle is that SBP increases linearly with age in industrialized societies.[6] Using this paradigm, the goal of early antihypertensive therapy is to delay or prevent the onset of hypertension, i.e., the age at which SBP exceeds 140 mmHg. In the Trophy trial (TRial Of Prevention of Hypertension), about 450 obese prehypertensive individuals (average baseline BP about 134/85 mmHg) were randomized to receive either placebo or candesartan (16 mg daily) for 2 years, followed by placebo for an additional 2 years in all subjects.[16] The primary dependent variable, the cumulative incidence of hypertension (BP >140/90 mmHg) at 2 years, was about 66% less with candesartan than placebo and the candesartan group still manifested 16% less hypertension at 4 years. TROPHY, which was too small to yield outcomes, nevertheless suggested that the relentless age-related increase in BP can be slowed by early interruption of the RAS.

PHARAO studied the value of ramipril in prehypertension.[17] Over 1000 participants with "high-normal" office BP (mean 134/84 mmHg) were randomized to ramipril or control for 3 years. Hypertension (BP >140/90 mmHg) occurred in 31% of the ramipril group and 43% of the control group (relative risk reduction 34.4%, $P = 0.0001$). Similar patterns were observed during ambulatory BP monitoring. Cerebrovascular and cardiovascular events were similar but cough was more frequent with ramipril (4.8% vs. 0.4%). The authors concluded that the treatment of patients with high-normal office BP with ACE inhibition reduced the risk of progression to overt hypertension and was well tolerated.

For comparison, lifestyle modifications have also been reported to delay the onset of hypertension. In the PREMIER study, over 18 months, behavioral interventions (reduced body weight, fat and sodium intake) and institution of the Dietary Approaches to Stop Hypertension (DASH) diet (increased fruit, vegetable, dairy, fiber, and mineral intakes) further reduced the odds ratio for developing hypertension compared with the advice--only control group (0.77, 95% CI 0.62–0.97 vs. 0.83, 95% CI 0.67–1.04).[18]

Prevention of albuminuria The double-blind ROAD-MAP trial (Randomized Olmesartan And Diabetes MicroAlbuminuria Prevention) studied the onset of diabetic nephropathy in over 4400 patients with type 2 diabetes over a median of 3.2 years. Mean pretreatment BP (136/81 mmHg) was 3.1/1.9 mmHg lower and microalbuminuria incidence was 23% lower in patients receiving olmesartan (40 mg daily) compared with placebo (8.2% vs. 9.8%, hazard ratio 0.77, 95% CI 0.63–0.94, $P = 0.01$).[19] Yet a secondary analysis revealed an infrequent but higher rate of cardiovascular death among patients with preexisting coronary heart disease taking olmesartan (11/564 vs. 1/540, $P = 0.02$). In the ADVANCE study (Action in Diabetes and Vascular Disease: Preterax and Diamicron

MR Controlled Evaluation), active antihypertensive treatment reduced the risk for overall renal events over 4.3 years by 21% (P <0.0001, microalbuminuria and microalbuminuria each P <0.003).[20] In a secondary analysis, very low SBP levels (<110 mmHg) were associated with the lowest rate of renal events, a pattern very similar to that observed for recurrent stroke in PROGRESS (Preventing Strokes by Lowering Blood Pressure in Patients With Cerebral Ischemia).[21] In the RASS study (Renin Angiotensin System Study) in type 1 diabetes, increases in microalbuminuria or glomerular mesangial fractional volume were not substantially different when renin-angiotensin blockers (enalapril or losartan) were compared with placebo.[22] In RASS, however, SBP was about 112 mmHg in all groups. Thus, when BP in type 1 diabetes is very low, there may be no benefit to RAS blockade.

Assessing hypertension-associated morbidity and mortality Clinical trials relating hypertension to target organ damage are usually based on aggregate endpoints that often mix morbidity and mortality and also include different disease mechanisms. An aggregate endpoint is usually a statistical convenience that increases the number of endpoints and reduces sample size in clinical trials (although global disease reduction is always a clinically relevant issue). In most studies, aggregate endpoints are overwhelmingly affected by IHD because IHD is more prevalent than the other hypertension-associated conditions. In the United States, MI occurs relatively commonly (about 1.2 million/year),[23] whereas hospitalized stroke (about 680,000/year),[24] heart failure (about 400,000/year),[25] and end-stage renal disease (about 130,000/year)[26] are somewhat less common. Usual selection criteria further enrich the population at risk for IHD. In depending so heavily on IHD to define benefit, investigators have consistently biased any conclusions related to other potential benefits. Complex endpoints also are confounded by different disease mechanisms, most commonly hypertension and occlusive atherosclerotic vascular disease, which is heavily dependent on cholesterol oxidation and Apo genetics. If one considers the complications driven most directly by hypertension (stroke, left ventricular hypertrophy, heart failure, CKD), different patterns of outcomes appear, as in SHEP (Systolic Hypertension in the Elderly Program), LIFE (Losartan Intervention for Endoint reduction), or HYVET (Hypertension in the Very Elderly Trial), where there were more strokes than MIs.[27-29] Based on this argument, it should not be surprising that a spectrum of interpretations regarding BP and antihypertensive drugs might occur. Readers should carefully weigh the selection criteria and each "secondary" outcome in addition to the composite in interpreting any clinical study.

Meta-regression studies If the benefits of antihypertensive drugs are solely related to the degree of BP lowering they achieve, the observed benefits of all antihypertensive drugs should follow a regression line defined by the 20/10 rule. Also, any drug class with additional benefit would be expected to deviate (to the good) from the meta-regression line. The Clinical Trialists Collaboration has used this approach to compare the value of BP reduction in the hypertension population and the relative merits of the individual antihypertensive drug classes.[30-32] The Trialists found an extremely strong correlation for virtually all classes of antihypertensive drugs (diuretics, β-blockers, ACE inhibitors, angiotensin receptor blockers, and calcium channel blockers) of the differences in BP between treatment arms and the corresponding reduction in mortality/morbidity in the individual clinical trials, with the slope of the relationship very closely approximating the 20/10 rule.[30-33] These strong trends persisted despite variations in study design, duration, endpoints, drug combinations, and other potential confounding issues and led to the conclusion that the primary protective benefit of antihypertensive therapy with any class of agents is the BP reduction itself. Yet imprecisions in measurement of the predictor variable or confounding of the outcome measure will intrinsically increase the data scatter and directly reduce the perceived strength of association. Also, the meta-regression technique only measures central tendencies, not those of potential outliers that are always present in the heterogeneous populations included in clinical trials. Thus, reliably defining effects "beyond BP" is difficult. Other methodological deficiencies (commonly selection bias, measurement imprecision, physiologic BP variability, and endpoint confounding – especially for mortality) also exist, leading to the need for extremely large populations to demonstrate central trends. Yet, it is undeniable that BP reduction is an extremely important goal in reducing premature CVD morbidity and mortality in the population.

The J-curve controversy The existence of a "J-curve," named for the apparent increase in CVD events observed at very high and very low levels of BP, remains actively debated and there is a persistent belief that lowering BP could cause cardiac hypoperfusion and ischemia in at-risk populations.[34] Many potential artifacts could contribute to the appearance of a J-curve, especially the use of composite endpoints along with confounding by age and other important comorbidities[35] or through nonlinear statistical interactions among risk factors.[36] There are also potentially important differences in the disease mechanisms themselves. It is still possible that there is a J-curve[11,37,38] but in general, there is less likelihood of increased risk with low SBP than with low DBP,[39,40] in part due to the impact of increased arterial stiffness and widened pulse pressure on cardiac afterload. No J-curve has been reported for recurrent stroke[21] or CKD.[20]

Stroke and chronic kidney disease In the PROGRESS study of stroke recurrence in individuals treated

TABLE 2 Results of a meta-analysis demonstrating the effects of antihypertensive drugs on various adverse events in nonhypertensive individuals with known hypertension-related comorbidities (adapted from Thompson et al.[45]; see text for full discussion)

Condition	Relative risk		Absolute risk reduction per 1000		NNT
	point estimate	95% CI	point estimate	95% CI	
stroke (all types)	0.77	0.61–0.98	–7.7	–15.2 to –0.3	130
MI	0.80	0.69–0.93	–13.3	–28.4 to 1.7	74
heart failure	0.71	0.65–0.77	–43.6	–65.2 to –22.0	23
CVD composite	0.85	0.80–0.90	–27.1	–-40.3 to –13.9	37
CVD mortality	0.83	0.69–0.99	–15.4	–32.5 to 1.7	65
all-cause mortality	0.87	0.80–0.95	–13.7	–24.6 to –2.8	73

Abbreviations: CI – confidence interval, CVD – cardiovascular disease, others – see TABLE 1

with ACE inhibitor and thiazide diuretic, retrospective analysis revealed that those with the lowest BP values post-stroke (mean 112/72) had the lowest stroke recurrence rate.[21] A similar trend was also noted for post-stroke patients with CKD.[41] Trends toward better renal outcomes at lower BP levels were found in the MDRD study (Modification of Diet in Renal Disease),[42] but apparently not in AASK (African Americans with Kidney Disease). Part of AASK was a comparison of BP targets;[43] those who achieved a lower BP (128/78 mmHg) did not experience a lower rate of deterioration in glomerular filtration rate (–2.21 [0.17] ml/min/1.73 m^2/y) compared with those with higher BP (141/85 mmHg; –1.95 [0.17] ml/min/1.73 m^2/y; $P = 0.24$). At the extreme of renal disease (dialysis patients), very low BP (<110/70 mmHg) is a poor prognostic sign.[44]

Diabetes In ACCORD (Action to Control Cardiovascular Risk in Diabetes), over 4700 diabetic participants were randomly assigned to intensive therapy (achieved SBP 119 mmHg) or standard therapy (achieved SBP 134 mmHg) with mean follow-up of 4.7 years. The annual rate of the primary outcome (nonfatal MI, nonfatal stroke, or death from cardiovascular causes) was 1.87% in the intensive group and 2.09% in the standard group (hazard ratio 0.88, 95% CI 0.73–1.06, $P = 0.20$), so the authors dutifully concluded that a SBP target <120 mmHg was not beneficial. This conclusion, however, belied the important finding that the stroke rate was lower in the intensive group (0.32% vs. 0.53%, hazard ratio 0.59, 95% CI 0.39–0.89, $P = 0.01$) – a major positive benefit. They also noted that serious adverse events occurred in 3.3% of the intensive group vs. 1.3% in the standard group ($P < 0.001$).

High-risk individuals A systematic Cochrane meta-analysis was performed in people "without clinically defined hypertension" to assess the potential benefits of antihypertensive drugs on secondary prevention of CVD morbidity and mortality.[45] Data from 25 trials were analyzed with the most salient data presented in TABLE 2. Results did not differ according to trial characteristics or subgroups defined by clinical history. The authors concluded that patients with clinical history of CVD but without hypertension experienced decreased risk of stroke, heart failure, composite CVD events, and all-cause mortality. No BP data were reported in this study and thus it is not fully clear how many had an antecedent history of hypertension (especially those with heart failure or prior MI), nor is it possible to relate the reported benefits to the degree of BP lowering. Despite its shortcomings, what is interesting about this study is the NNT analysis: about 74 high-risk individuals needed to be treated with antihypertensive drugs to prevent 1 MI and about 130 to prevent a stroke. By comparison, about 400 individuals in the general population would require treatment to prevent 1 CVD event (TABLE 1). The difference, of course, is the higher risk level in those with underlying CVD. Overall, populations with the highest risk are most efficiently treated with antihypertensive drugs, as evidenced by the fact that the NNT for a nonhypertensive, high-risk individual is less than that for a person with stage 2 hypertension.

What are the implications for clinical care? Answer: Antihypertensive medications prevent and treat high-risk conditions associated with hypertension (cardiovascular, cerebrovascular, and renal diseases); the decision to use antihypertensive drugs in individuals in the "nonhypertensive" range is fully justifiable but requires adequate clinical experience and judgment to assess risks and benefits.

To summarize the foregoing arguments:

1 There are several pharmacologic mechanisms by which antihypertensive drugs can benefit patients: first by lowering BP but secondly by treating hypertension-associated comorbidities such as IHD, heart failure, or CKD.

2 The risks associated with BP are continuous over a very wide range, including values below 140/90 mmHg.

3 There is evidence of enhanced benefit of antihypertensive drugs at all BP levels in high-risk conditions, including delay or prevention of hypertension in prehypertensives, delay or prevention of albuminuria in diabetics, and improved morbidity and mortality in individuals with hypertensive target organ damage (heart disease, stroke, kidney disease).

A general recommendation is that consideration be given to the use of antihypertensive drugs in individuals whose BP values are below 140/90 mmHg but have enhanced risk for subsequent cardiovascular, cerebrovascular, and renal diseases. A risk-benefit analysis based on medical evidence as well as practitioner experience and judgment are the essential components to ensure optimal patient outcomes.

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Korzyści ze stosowania leków przeciwnadciśnieniowych u osób z ciśnieniem tętniczym <140/90 mm Hg

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SŁOWA KLUCZOWE

leki przeciwnadciśnieniowe, stan przednadciśnieniowy, wyniki

STRESZCZENIE

Leki przeciwnadciśnieniowe stosuje się w celu obniżenia ciśnienia tętniczego, ale ostatecznie ich rzeczywista wartość polega na zmniejszaniu chorobowości i śmiertelności (choroba sercowo-naczyniowa, mózgowo-naczyniowa i choroby nerek). Granicę rozpoznawania nadciśnienia tętniczego ustalono na wartość 140/90 mm Hg, chociaż rzeczywista zależność pomiędzy wysokością ciśnienia tętniczego oraz niekorzystnymi zdarzeniami sercowymi i mózgowo-naczyniowymi ma charakter ciągły. Badania obserwacyjne wykazały silną korelację logarytmiczno-liniową pomiędzy wysokością ciśnienia tętniczego w granicach 115/75–185/115 mm Hg a śmiertelnością z powodu choroby niedokrwiennej serca lub udaru mózgu. Badania kliniczne i metaanalizy wyraźnie wykazały korzyści stosowania leków przeciwnadciśnieniowych u osób „bez nadciśnienia tętniczego": opóźnienie lub zapobieżenie wystąpieniu nadciśnienia tętniczego i mikroalbuminurii oraz zmniejszenie chorobowości i śmiertelności z powodu choroby niedokrwiennej serca, udaru mózgu i przewlekłej choroby nerek. Nie jest to zaskoczeniem, jesli weźmie się pod uwagę, że różne klasy leków przeciwnadciśnieniowych dają wiele potencjalnie korzystnych efektów. Utrzymuje się obawa, że zbyt agresywne leczenie nadciśnienia tętniczego może zwiększyć ryzyko u osób z chorobą niedokrwienną serca, ale tzw. efekt krzywej J nie zawsze obserwowano w badaniach klinicznych. Stosowanie leków przeciwnadciśnieniowych u chorych z grupy ryzyka, którzy mają ciśnienie niższe niż tradycyjna wartość progowa (140/90 mm Hg), jest w pełni uzasadnione, chociaż decyzja o leczeniu wymaga odpowiedniego doświadczenia klinicznego oraz pełnej oceny ryzyka i korzyści związanych z leczeniem.

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