

# Cardiovascular risk reduction in hypertension: A new definition opens new therapeutic opportunities

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## SUMMARY

The ultimate goal of hypertension therapy is the prevention of atherosclerotic cardiovascular (CV) complications. Numerous clinical trials have shown that blood pressure (BP) lowering reduces CV risk by approximately 20% - 25% for myocardial infarction, 35%-40% for stroke and 50% for heart failure. Medical society cannot be proud for the risk reduction rates achieved. It is supported nowadays that a 65 % risk reduction in hypertensives and 80% in general population is both logic and feasible. Recently furthermore, questions have been raised concerning the sensitivity of BP as a marker or risk factor for CV events, and even more whether BP is really a cause or a consequence of CV disease. There is no doubt that a better protection using new preventive strategies is needed to achieve this target. As a result there is a shift in antihypertensive therapy focusing mainly on global CV risk reduction rather than on BP levels per se. In this review, after a brief introductory reference to traditional antihypertensive therapy we discuss in detail the data on a recently suggested new definition and classification of hypertension. The rationale of physiology for treating concomitant risk factors and the importance of focusing on global CV risk reduction beyond BP control are also presented. Finally the rationale and existing evidence for new therapeutic concepts and especially on statin's use in high risk hypertensives are also discussed.

## INTRODUCTION

As late as in the 1940s and early 1950s elevated blood pressure (BP) was considered to be a natural response to provide perfusion of vital organs. Experts suggested that lowering high BP might do more harm than good; others discussed hypertension simply as a benign disease. Nowadays the association of hypertension with cardiovascular (CV) morbidity and mortality is well established. Abundant epidemiological data have shown that the risk of CV disease, starting at  $\geq 115/75$  mmHg, rises with increasing BP levels, in a strong, independent, graded and continuous manner. Hypertension remains extremely common, with an estimated prevalence of 30% of the adult population, of whom only about 30% have their BP controlled to the recommended level of  $< 140/90$  mmHg. Obviously, hypertension is not yet under control, it is under-controlled<sup>1-3</sup>.

Traditionally antihypertensive therapy must include **lifestyle modification**<sup>4-9</sup> and strategies to improve **adherence**<sup>10</sup>. As early and aggressive BP lowering leads to long-term CV risk reduction, there is no time to waste in hypertension treatment: **the sooner is the better**<sup>11-13</sup>. Treatment at target levels is a critical point but usually is not achieved even in clinical trials. Regarding the target level there is no doubt today that **the lower is the better**. This has been clearly demonstrated in the meta-analysis by Lewington S et al<sup>14</sup>, as it is seen on Figure 1. The BP target can be achieved usually using combinations of drugs and this is why today the failure to titrate or combine medications despite the knowledge that the patient is not at target BP, represents clinical inertia and must be overcome. Although the main benefit with antihypertensive therapy is due to BP lowering per se, there is a

growing evidence and a strong pathophysiologic basis suggesting that some antihypertensive therapies, particularly those based on renin-angiotensin-aldosterone system (RAAS) blockade, can reduce CV disease risk with a manner, at least partially, independent of BP lowering. **Modulation of RAAS** along with BP lowering is probably the best selection due to beneficial pleiotropic effects on metabolic profile and especially on the vasculature. A recent meta-analysis by Wier R (Fig 2) comparing RAAS vs non RAAS regimens revealed a significant benefit on the end point of CV death reduction (22 %, 13 % and 24 % respectively) in studies HOPE, LIFE, ASCOT where the BP advantage was gained by a RAAS regimen, while there was not any benefit in studies where the BP lowering was achieved by a non RAAS regimen such as VALUE and ALLHAT<sup>15-18</sup>.

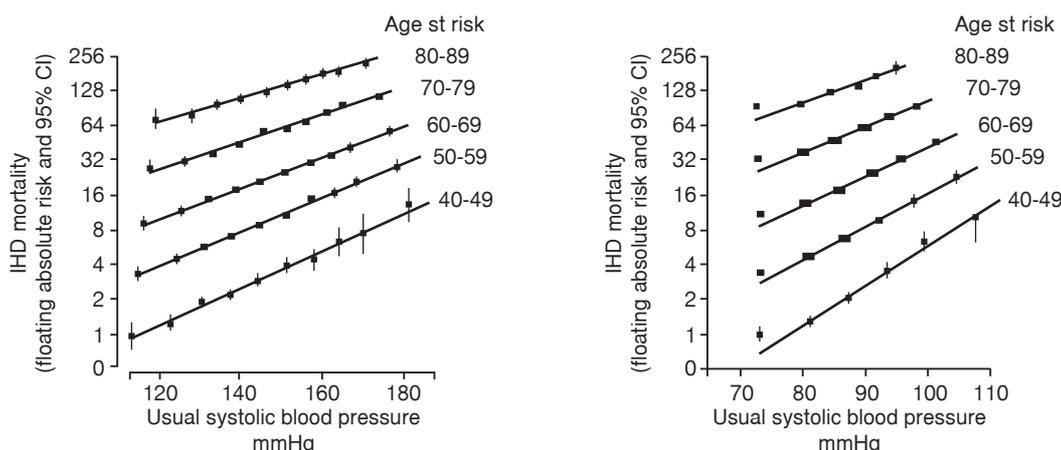


Fig. 1. Ischemic heart disease rates by Systolic BP, Diastolic BP and age (adapted from Lewington et al, Lancet 2002; 360:1903-1913).

	Hope n=9,297	Allhat n=33,357	Life n=9,193	Value n=15,245	ASCOT n=19,342
Age (years)	66	67	67	67	63
CAD (%)	80	25	16	45	17
Diabetes	39	36	13	33	22
SBP Difference	-10 mmHg ABPH -3 mmHg Office	-3 to -5 mmHg	-1.3 mmHg	-2 to -4 mmHg	-2,9 mmHg
BP Advantage Regimen	RAAS	Non-RAAS	RAAS	Non-RAAS	RAAS
End Point: CV Death	-22%	No Difference	-13%	No Difference	-24%

Fig. 2. RAAS versus Non-RAAS regimens on cardiovascular endpoints (adapted from Wier et al, J Clin Hypertens 2006; 8: 99-105).

Yet, the precise physiologic mechanisms by which hypertension increases CV risk and antihypertensive therapy lowers it remain unclear. Despite the robust association of hypertension with CV risk in populations, some patients with hypertension do not experience CV events during long life spans and CV events occur sometimes in non-hypertensives. Although atherosclerosis usually occurs clinically in middle-aged, the underlying pathology begins in the first decade of life. Hypertension starts in the childhood. It is widely accepted today that hypertension is associated with a constellation of other CV risk factors, such as the metabolic syndrome components, endothelial dysfunction, arterial stiffness and nephropathy, indicating its role in a multifactorial disease process. These data have led to a new definition and classification of hypertension and development of new therapeutic concepts giving importance on **global risk reduction**.<sup>19-24</sup>

## NEW DEFINITION AND CLASSIFICATION OF HYPERTENSION

A new definition of hypertension has recently been published which evolves beyond the traditional equation of hypertension solely with elevated BP levels. Instead it integrates CV risk factors, early disease markers and overt CV disease into the definition and classification. Hypertension is not only equal to elevated BP levels. The president of ASH Thomas D Giles, in his speech at the last ASH meeting emphatically made clear that the word hypertension must be almost deleted as it has no meaning<sup>23</sup>. This shift in focus intends to assist clinicians in assessing global CV risk, regardless of BP level and in identifying and managing hypertension as an earlier disease progress.

Hypertension must be considered as a progressive CV disorder that leads to functional and structural vascular abnormalities that damage the vasculature, heart, kidneys, brain and other organs leading to morbidity and premature death. Since early markers of CV disease are often present even before BP elevation is observed, hypertension cannot be classified only by discrete BP thresholds. Individuals considered not to have hypertension are only those who have no CV risk factors, no identifiable early risk markers, no target-organ damage, while in parallel their resting BP levels are usually <120/80 mmHg.

It is obviously practical to describe the progres-

sion of hypertension in stages. At all stages, treatment should aim to protect the arterial wall, prevent a rise in BP and lower BP when elevated. The following stages of hypertensive disease can be identified:

Stage I hypertension is the earliest identifiable stage of hypertensive disease and generally arises from circulatory, vascular or renal adaptations to environmental or genetic factors. This stage is characterized by the presence of CV risk factors or early disease markers, i.e. early signs of functional or structural changes in the heart and small arteries. There is not any evidence of target-organ damage and BP levels typically range between 120/80 mm Hg and 139/89 mmHg.

Stage II hypertension indicates that progressive disease has developed, accompanied with functional and structural changes in the heart and vasculature. Individuals with stage II hypertension usually have BP levels between 140-159 mm Hg and 90-99 mm Hg. In addition, they have multiple risk factors, numerous disease markers and evidence of early target – organ damage, such as left ventricular hypertrophy or a wide pulse pressure. Risk factors that are associated with stage II hypertension, if not attenuated, continue to contribute to progressive target-organ disease.

Stage III hypertension is an advanced stage of the hypertensive continuum in which overt target-organ disease is often present and CV events may have already occurred. Individuals on stage III generally have sustained resting BP levels  $\geq$ 140/90 mm Hg, although all individuals with clinical evidence of overt hypertensive target – organ damage should be included in this category, regardless of BP levels.

Hypertension is best described by changes in the arterial wall rather than only by elevated BP levels. This assumes that BP elevation is an insensitive and nonspecific surrogate for the vascular changes and that the changes in the artery wall, represent better the disease process. By utilizing CV status in addition to BP, clinicians will likely give a greater emphasis on identifying and managing hypertension at an earlier stage in the disease process with a greater focus on treatment aimed at protecting the arterial wall and preventing increases in BP levels. Designating individuals with high-risk profiles and BP levels <140/90 mmHg as hypertensive, for example, assists providers and patients in recognizing that a disease state already exists, allowing easier identification of individuals with early hypertensive CV disease. Identifying and control-

ling coexisting modifiable CV risk factors is critical and hypertension screening should be part of the overall global risk assessment. The new definition of hypertension thus offers a more global risk-based approach for identifying those individuals at any level of BP who have a reasonable likelihood of developing future CV events. By identifying hypertension in individuals with high-risk profiles independently of BP levels and by focusing on the level of the blood vessel, the overall care of patients at risk for CV events should significantly improve<sup>23,24</sup>.

## NEW THERAPEUTIC CONCEPTS

### *a. The rationale of physiology for treating concomitant risk factors*

In clinical practice, a significant shift in hypertension therapy is the recognition of the interaction of CV risk factors. As global risk profile is essential for CVD prevention, application of new treatment strategies must focus on this topic. Hypertension from the beginning and in all stages is associated with many other CV risk factors. It is now well accepted that the nine most important classical risk factors (hypertension, smoking, obesity, physical inactivity, dyslipidemia, diabetes mellitus, microalbuminuria, age, and family history of premature CVD) account for the 90 % of CVD.

The patients with multiple risk factors can be identified by history, physical examination, biomarkers, risk calculators and imaging modalities. Several tools have been developed to help identify individuals at CV risk. CV risk assessments are usually carried out using risk charts or calculators that are based on epidemiologic data. The Framingham Heart Study risk equation estimates the CV disease risk over 10 years, based on 7 risk factors- age, gender, SBP, TC, HDL-C, smoking and diabetes. Regional and country-specific risk calculators are becoming increasingly available and should improve risk estimation in specific populations. Antihypertensive therapy should therefore be coordinated with other preventive measures; all strategies used to prevent or manage CV risk factors or early disease markers should be considered as part of the overall regimen to reduce global risk. Global risk reduction is probably the most important target of hypertension treatment<sup>25-28</sup>.

The most common and probably most important coexisting risk factor with hypertension is dy-

slipidemia. Hypertension and dyslipidemia occur commonly in unison than cannot be attributed to chance, as almost 65 % of hypertensives have also high cholesterol. This is not simply a co-existence but there is a causal interaction among these two factors. There is an independent and causal relationship (not simply association) between baseline lipids and hypertension. This relation is not constant. The effects of high BP are more prominent in low cholesterol levels while the effects of cholesterol are more prominent in lower BP levels. Hypercholesterolemia increases AT<sub>1</sub> receptor expression and this effect is blocked by statins. On the other hand AII increases LOX-1 receptors expression an effect which is blocked by RAAS blockade. The presence of dyslipidemia increases the risk of developing hypertension in later life. Thus, multiple risk factors for cardiovascular disease generate the vascular disease phenotype. High BP and high cholesterol are often considered as separate “disease entities” and the interaction of these risk factors in the pathogenesis of vascular disease has been poorly recognized and is certainly underestimated. At the biological level, there is considerable potential for blood pressure to augment the LDL-C mediated vascular damage. This can occur via enhanced oxidation of LDL-C and the enhanced pressure-mediated migration of LDL-C through the vessel wall. Similarly, LDL-C, by virtue of its adverse effects on endothelial function, has the capacity to generate and/or augment the development of hypertension. This effect has been observed in children with familial hypercholesterolaemia and even in adults with modest elevations of LDL-C. On the other hand, men in the highest quintile of TC, non-HDL-C and TC/HDL-C ratio have increased risks of developing hypertension. Men in the highest quintile of HDL-C have a 32 % decreased risk of developing hypertension. Moreover, by influencing large and small artery function, LDL-C can modify central aortic hemodynamics and pressures, thereby contributing to pressure-mediated vascular injury. Finally, in the later stages of vascular disease, there is a clear association between the vulnerable lipid-laden plaque rupture and haemodynamic stresses resulting in the process of plaque rupture and clinical events onset.

This synergism between LDL-C and elevated blood pressure for the development of vascular dysfunction highlights its importance in the spectrum of hypertensive vascular disease, ranging from early

disturbances in endothelial function and the generation of hypertension, to overt clinical consequences. These observations also highlight the need for a greater emphasis on multiple risk factor intervention to target the continuum of hypertensive disease from its primitive appearance to overt cardiovascular disease. It is nowadays certain that a 10% of BP plus a 10% of lipid reduction leads to 45% CV risk reduction (10+10 = 45!!). Data from recent clinical trials support this approach<sup>29-33</sup>.

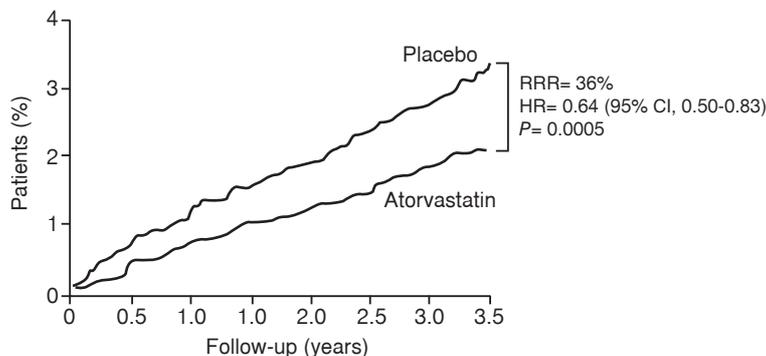
### ***b. The rationale for evidence based medicine on treatment of concomitant risk factors***

The benefits of cholesterol lowering with statins have been demonstrated in numerous large-scale randomized placebo-controlled trials. Several prospective observational studies have shown that overall cardiovascular risk in hypertensive patients is compounded with the presence of additional risk factors. However there was no trial addressing benefits of lipid lowering for primary prevention of CHD in hypertensive patients not conventionally deemed dyslipidemic. Furthermore, there was less than expected CHD prevention using standard BP-lowering therapy although it is obvious that combination of risk factors synergistically cause CHD. This fact led to new therapeutic opportunities and so new studies have been coordinated<sup>34-38</sup>.

The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) is the first which has been published regarding this topic. The rationale for ASCOT coordination was the fact of high prevalence of dyslipidemia in hypertensives and the fact that a combination of risk factors synergistically causes CHD while there is less than expected CHD prevention using standard BP-lowering therapy. Furthermore,

there was no trial specifically addressing benefits of lipid lowering in primary prevention of CHD in hypertensive patients not conventionally deemed dyslipidemic. The ASCOT-BPLA provided further evidence of differences between therapeutic strategies. This study compared the effect of non-fatal myocardial infarction and fatal CHD of combination of atenolol with thiazide versus amlodipine with perindopril, showing that a mean difference of 2.7 mmHg in the decrease of SBP and 1.9 mmHg in DBP between treatment arms favoring the combination of ACE inhibitor and calcium antagonist was sufficient to achieve a significant reduction of 14 % of the relative risk of total coronary events. In addition, the risk of new onset diabetes was significantly lower. The trial was stopped prematurely, because of mortality difference between the two treatment arms.

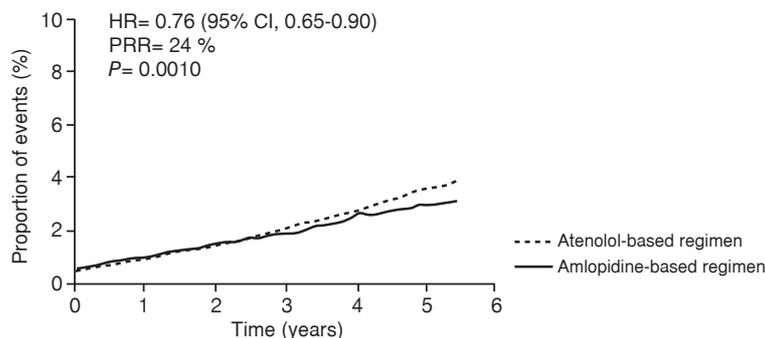
In the ASCOT-LLA (Lipid Lowering Arm) in a subgroup of participants with total cholesterol levels <250 mg/dL, a statin (atorvastatin 10 mg) was compared with placebo. Both arms of the trial were stopped prematurely because of unequivocal benefits in the treatment arm. Survival curves were separated almost immediately with significant difference at 90 days. Total mortality and cardiovascular mortality were reduced significantly in favor of the amlodipine-based regimen (11% and 24%, respectively- Fig 3). There was a non-significant reduction of 10% in the primary end point of nonfatal MI and fatal coronary heart disease (best explained by a lack of power owing to stopping the trial early). A 14 % composite coronary end point and a 23 % stroke reduction were achieved by the amlodipine-based regimen, compared with those assigned the atenolol-based strategy. In addition, the



Nonfatal MI and fatal CHD

Sever PS et al. *Lancet*. 2003;361:1149-58.

**Fig. 3.** Atorvastatin reduces primary outcome in hypertensive patients (ASCOT-LLA).



Number at risk						
Amlodipine-based regimen (263 events)	9639	9544	9441	9322	9167	8078
Atenolol-based regimen (342 events)	9618	9532	9415	9261	9085	7975

Dahlöf et al, ASCOT Investigators. *Lancet*. 2005;366:895-906

**Fig. 4.** ASCOT-BPLA reduction in Cardiovascular Mortality.

newer amlodipine –based strategy was associated with 30% fewer cases of new-onset diabetes. ASCOT-BPLA demonstrated greater benefits of new vs old drugs both in lowering BP and preventing CVD. The improved BP control with new drugs explains some, but not all, benefit gained. It is the beyond blood pressure control effect of these drugs.

Further analyses suggest the possibility of synergy between atorvastatin and the amlodipine-based treatment strategy. ASCOT-LLA extended the benefit of lipid lowering to hypertensives regarding coronary heart disease and stroke as well. Primary outcomes (non fatal myocardial infarction and fatal coronary disease events) were reduced by 36% while stroke was reduced by 27% compared to placebo (Fig. 4). The significant lessons gained from this study led to changes in the European and other medical societies guidelines on optimal management of the hypertensive patient<sup>39,-42</sup>. The recently published Canadian Recommendations for BP control are shown on Table 1. As it is seen on the table they tribute special importance on the meaning of lipid lowering for additional improvements

in CV outcomes and especially on vascular protection gained by statin use. Canadian recommendations for optimal vascular protection and proper statin use are shown on Table 2. Statin use is strongly recommended in high risk hypertensives with at least 3 concomitant CV risk factors<sup>43,44</sup>.

**Table 1.** Canadian Hypertension Education Program recommendations (CHEP) 2006

- Hypertension starts in the childhood
- From the very beginning hypertension is associated with multiple CV risk factors
- The rennin-angiotensin and sympathetic nervous systems facilitate the association of BP elevation with other risk factors
- Prompt, intensive, early BP reduction improves CV outcomes
- Lipid lowering leads to additional improvements in CV outcomes in treated hypertensives
- Improved patients adherence and lifestyle modification is needed
- Global Vascular Protection (Statins if 3 or more additional CV risks, Aspirin once BP is controlled)

**Table 2.** Statins and Vascular Protection for Hypertensive Patients (CHEP 2006)

Statins are recommended in high-risk hypertensive patients with established atherosclerotic disease or with at least 3 of the following criteria:

Male	Total C / HDL-C ratio >6	Previous stroke or TIA
Age >55 years	LVH	Family history of premature CV risk
Smoking	ECG abnormalities	Microalbuminurea or Proteinurea
Type 2 diabetes	Peripheral vascular disease	

## CONCLUSIONS

Many large-scale hypertension trials completed over the past few decades led to the consistent conclusion that reaching the BP goal, regardless of the therapy used, is the most effective way to reduce CV risk. However, hypertension is a multifactorial disorder associated with many other risk factors. In addition a new definition of hypertension integrates CV risk factors into classification and treatment of hypertension, emphasizing their significance on risk reduction. These new data support the concomitant use of newer BP drugs and statins especially in patients with complicated hypertension or with more than three additional risk factors. Antihypertensive treatment should depend on global assessment of risk and not on individual risk factors or BP lowering per se<sup>44</sup>. Whilst BP lowering is undoubtedly beneficial, the real target must be vascular protection and the global CV risk lowering. We must go beyond BP and the most effective way to go “beyond BP” is to add a statin.

Finally, hypertension is nowadays somehow reconsidered, as new data have led to questions concerning the sensitivity of BP alone as a marker or risk factor for CV events in individuals and led to questions on whether BP is a cause or a consequence of CV disease. This last question sounds strange and somewhat mysterious but it is very attractive and remains to be proved. One should consider that in science, as in a romance, things are often beautiful when they are at least somewhat mysterious. This is the beauty of medical science!

## ΠΕΡΙΛΗΨΗ

**Αντωνακούδης ΧΓ, Πουλημένος ΑΕ, Αντωνακούδης ΓΧ. Μείωση καρδιαγγειακού κινδύνου στην υπέρταση: Νέος ορισμός και νέες θεραπευτικές δυνατότητες. *Arterial Hypertension* 2007; 16: 91-99.**

Τελικός σκοπός της αντιυπερτασικής αγωγής είναι η πρόληψη των καρδιαγγειακών επιπλοκών. Κλινικές μελέτες έχουν δείξει ότι η μείωση των επιπέδων της αρτηριακής πίεσης (ΑΠ) μειώνει τον κίνδυνο εμφράγματος κατά 20-25%, του αγγειακού εγκεφαλικού επεισοδίου κατά 35-40% και της καρδιακής ανεπάρκειας κατά 50% περίπου. Η ιατρική κοινότητα δεν θα πρέπει να είναι ικανοποιημένη με αυτά τα ποσοστά επειδή σήμερα πιστεύεται ότι είναι δυνατή μείωση του κινδύνου έως και 80% στο γενικό πληθυσμό και 65% στους υπερτασικούς. Είναι προφανές ότι χρειάζεται βελτίωση των στρατηγικών μείωσης

του κινδύνου και σήμερα υπάρχει σημαντική αλλαγή κατεύθυνσης στους στόχους της αντιυπερτασικής αγωγής, καθώς φαίνεται ότι πρωταρχικός στόχος πρέπει να είναι η μείωση του συνολικού καρδιαγγειακού κινδύνου και όχι μόνο τα επίπεδα ΑΠ. Σήμερα εγείρονται ερωτηματικά ως προς την ευαισθησία της υπέρτασης ως δείκτη ή παράγοντα κινδύνου καρδιαγγειακών συμβαμάτων καθώς ακόμη και για το αν η υπέρταση είναι το αίτιο ή το αποτέλεσμα της αθηροσκλήρωσης. Στην παρούσα ανασκόπηση γίνεται αρχικά σύντομη αναφορά στην κλασική και σύμφωνα με τις ισχύουσες οδηγίες ακολουθούμενη σήμερα στρατηγική. Στη συνέχεια γίνεται αναφορά αναλυτικά σε ένα νέο ορισμό και κατηγοριοποίηση της υπέρτασης που αναφέρονται πρόσφατα στη βιβλιογραφία. Σύμφωνα με τα νέα δεδομένα στον ορισμό της υπέρτασης, πέρα από τα επίπεδα της ΑΠ, δίνεται μεγάλη σημασία στους συνυπάρχοντες παράγοντες κινδύνου, στην παρουσία των νέων βιολογικών δεικτών αγγειακής βλάβης καθώς και την ύπαρξη εγκατεστημένης αθηροσκληρωτικής νόσου. Παρουσιάζονται το σκεπτικό, τα παθοφυσιολογικά δεδομένα και η σημασία της στόχευσης στο επίπεδο του συνολικού καρδιαγγειακού κινδύνου πέραν των επιπέδων της ΑΠ. Ιδιαίτερα τονίζεται η σημασία και η υπάρχουσα τεκμηρίωση για τη χρήση των στατινών σε υπερτασικούς ασθενείς υψηλού κινδύνου.

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