New markers of hypertensive disease

Focus on arterial stiffness

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Introduction

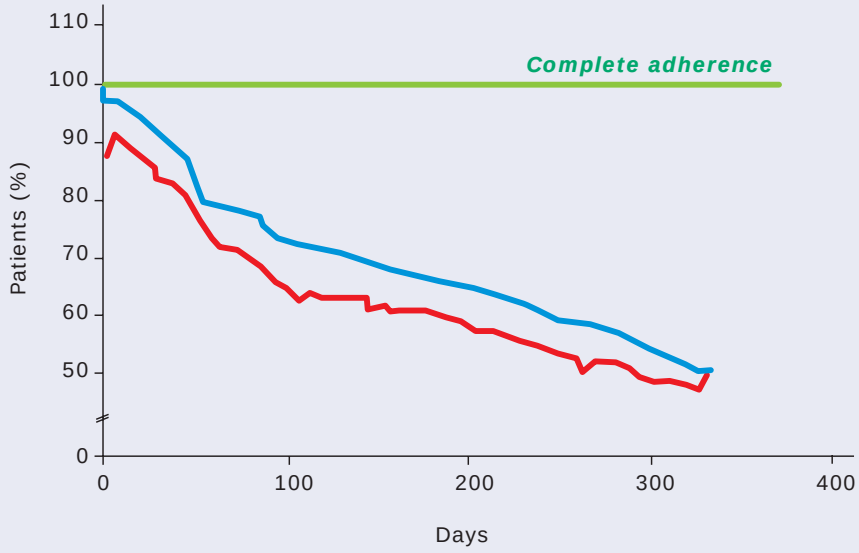
Despite compelling evidence for the efficacy of primary prevention, cardiovascular disease (CVD) remains the main cause of mortality in Europe[1]. The EURIKA study, a cross-sectional study conducted simultaneously in 12 European countries during 2009, demonstrated that many patients with treated CVD risk factors remained inadequately controlled. In fact, of 4.407 patients with dyslipidaemia, 74.4% were treated with lipid-lowering drugs, but target total and LDL cholesterol levels were reached *only* by 41.2% of treated patients. Among 2.046 patients with type 2 diabetes, 87.2% were treated with antidiabetic drugs, but the recommended HbA1c level of 6.5% was reached by 36.7% of treated patients only. Of 3.324 patients with a diagnosis of obesity prior to study enrolment, 92.2% were on lifestyle treatment (weight reduction advice) and the target of BMI<30 kg/m^2 was reached by 24.7% of these patients. Finally, the percentage of treated patients with 1, 2, or the 3 main CVD risk factors (hypertension, dyslipidaemia, diabetes) at goal was 41.3, 18.6, and 3.7%, respectively. There were a substantial proportion of patients remaining at high CVD risk (35–39% for the different individual risk factors) among those who achieved specific treatment goals, probably because of under consideration of other risk factor other than the main one[1].

The most recent US survey data shows that high BP awareness, treatment, and control rates have improved from 69%, 53%, and 26%, respectively, at the time of the 1988 to 1994 Nutrition Health and Examination Survey to 76%, 65%, and 37% between 2003 to 2004. Anyway, despite the greater availability of effective antihypertensive agents, about 65% of patients with hypertension receive the indicated cares and only 50% of patients for whom drug treatment is initiated persist on treatment 1 year later[2].

The consequences of nonadherence are serious because of the resulting poor clinical outcomes and preventable health care costs. Results from a meta-analysis by Di Matteo[3] showed a 27% difference in clinical outcome between patients with low *vs* high adherence. Cherry and colleagues[4] assessed the benefit of "*ideal*" over "*typical*" adherence in patients with hypertension and hyperlipidemia and found a nearly double relative risk (13.3 *vs* 25 events per 100 patient-years over 3 years) of myocardial infarction, angina, and stroke in patients who showed no adherence *vs* those who showed ideal adherence (**figure 1**).

In addition to gold standard therapy, improvement in smoking cessation strategies, effective healthy diet advice, weight reduction advice in obese patien-

Figure 1. Fall in adherence because of discontinuation of treatment (——) or because of poor execution of dosing regimen (——). (From Vrijens B et al 2008[63]).



ts, and physical activity advice may substantially increase risk factors control[1].

The role of emerging markers

Hypertension, defined as sustained elevation of brachial blood pressure, is a major risk factor for cardiovascular disease, and reduction of brachial blood pressure decreases cardiovascular events, particularly stroke[6]. But to stratify CVD risk, we have to consider many other risk factors. In hypertensive individuals, renal subclinical organ damage is associated with a 10-year risk of cardiovascular events of 20% or more. Data from the ELSA[7] have shown that baseline carotid intima–media thickness (IMT) predicts cardiovascular events independent of BP. Even asymptomatic peripheral vascular disease as detected by a positive ankle-brachial index has prospectively been found to be associated in men with an incidence of cardiovascular events approaching 20% in 10 years[8,9].

Among these traditional risk factors, pulse wave velocity (PWV) and central aortic pressure (CAP) are gaining importance. Pulse wave velocity, a measure of vascular stiffness, has been related to cardiovascular risk[61] in hypertensive patient[10], in the elderly[11], in patients with end-stage renal disease[12], and in population-based samples[13]. CAP can be measured by noninvasive techniques[14] and potential evidence of greater prognostic importance of central aortic than brachial pressures has been obtained in treated hypertensive patients[15]. Increased arterial stiffness causes a premature return of reflected waves in early systole, increasing central PP and systolic BP, leading to an increased load on the left ventricle and greater myocardial oxygen demand. Arterial stiffness, wave reflections, and central pressure can serve in clinical practice as "*intermediate*" or "*surrogate*" end points for cardiovascular events.

In fact, these parameters have an independent predictive value for cardiovascular morbidity and mortality[5]. In the Copenhagen County population, an increased pulse wave velocity (PWV >12 m/s) was associated with a 50% increase in the risk of a cardiovascular event[16]. Independent predictive value of PWV for cardiovascular events has been shown in Japanese men followed for 8.2 years[17]. The independent predictive value of aortic stiffness has been demonstrated after adjustment to classic cardiovascular risk factors, including brachial PP, *suggesting that aortic stiffness adds value to a combination of cardiovascular risk factors*[19]. *This finding may be related to the fact that aortic stiffness integrates the damage to the aortic wall of cardiovascular risk factors over a long period, whereas BP, glycemia, and lipids can fluctuate over time and the values recorded at the time of*

risk assessment may not reflect the true damage to the arterial wall[60]. Another explanation may be that the identification of aortic stiffness reveals the translation from risk factors to real risk in any patients[19,20].

The most important study to date to examine the relative importance of central and brachial blood pressures has been the Conduit Artery Function Evaluation (CAFE) study of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) hypertension trial[21]. Although brachial blood pressure was reduced to a similar extent in both the atenolol/thiazide and amlodipine/perinopril arms of the CAFE study, a significantly greater reduction in central aortic pressures and AIx was achieved with the amlodipine regimen than with the atenolol regime. Furthermore, both brachial and central pulse pressures were similarly to a post hoc-defined composite outcome (new car-

Figure 2. Relation between 10-year CVD risk and aortic pulse wave velocity. (From Blacher J et al 1999[61]).

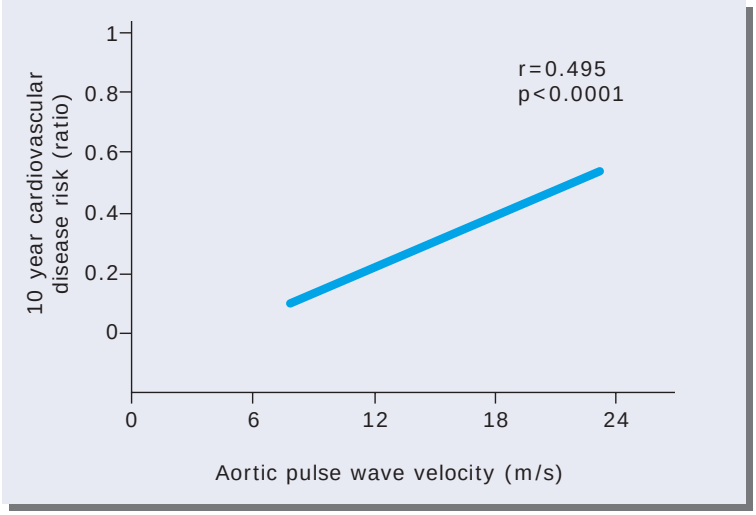
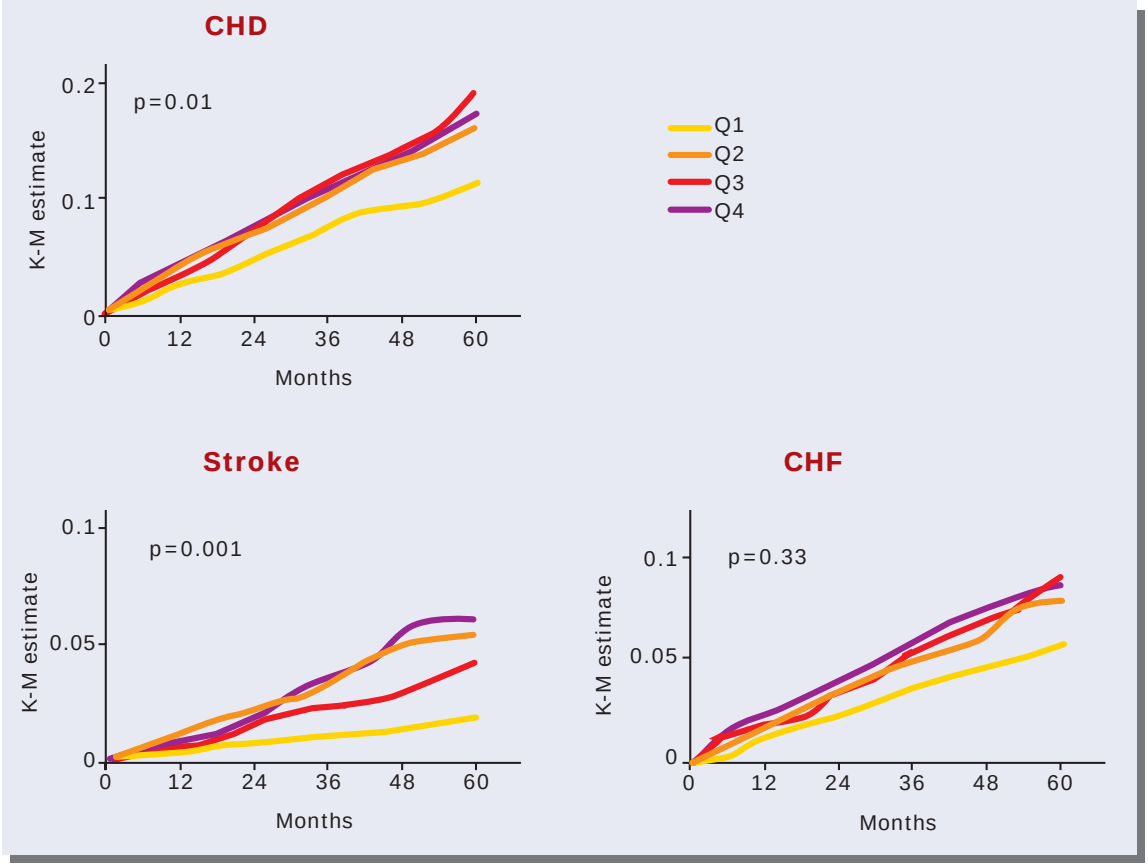


Figure 3. Kaplan-Meier estimates of CHD (top), stroke (middle), and CHF (bottom) by a PWV quartile. (From Sutton-Tyrrel K et al 2005[62]).



diovascular events, cardiovascular procedures, renal impairment) independent of other risk factors[5] (**figure 2 and figure 3**). Although measures of stiffness are useful in predicting the occurrence of cardiovascular events, the value of reduction in arterial stiffness as a measurement of the reduction by treatment of the risk of such events has not yet been unequivocally proven. The only clinical evidence that reducing arterial stiffness is associated with a decreased risk of cardiovascular events was obtained in ESRD patients by Guerin et al[22]. In a mean follow-up of 50 months, the absence of PWV decrease in response to BP decrease was one of the predictors of all-cause and cardiovascular mortality, together with increased left ventricular mass, age, and preexisting cardiovascular disease. After adjustment for all confounding factors, the risk ratio for the absence of PWV decrease was 2.59 for all-cause mortality and 2.35 for cardiovascular mortality. However, the effect of aortic stiffness attenuation on cardiovascular morbidity and mortality remains to be established in other populations. Indeed, in the REASON study, the combination of perindopril and indapamide significantly attenuated carotid wave reflections[23], resulting in a selective decrease in central systolic BP and PP, and leading to a related reduction in left ventricular hypertrophy[24]. This effect was not observed in the atenolol treatment arm, in which carotid PP was not equally reduced. *The results of the CAFE study suggested that the positive effect of renin-angiotensin system blockers beyond BP control could be attributed to a greater effect on reduction of arterial stiffness*[21].

Usual therapies and their limitations

The 2007 ESH/ESC guidelines underline that, no matter which drug is employed, monotherapy can effectively reduce BP in *only a limited number of hypertensive patients, most of whom require the combination of at least two drugs to achieve BP control*[26]. *A meta-analysis of 42 studies has shown that combining two agents from any two classes of antihypertensive drugs increases the BP reduction much more than doubling the dose of a single drug*[25]. The 2007 ESH/ESC guidelines[26] recommend the combination of two drugs to be considered as initial treatment whenever hypertensive patients have a high initial BP or are classified as being at high/very high cardiovascular risk because of the presence of organ damage, diabetes, renal disease, or a history of cardiovascular disease.

Strategies to improve both efficacy and adherence to treatment

The combination of an ACE inhibitor, perindopril, and the diuretic indapamide had already been shown in the PROGRESS study to have a greater BP lowering effect than the ACE inhibitor alone and, in parallel, a much greater preventive effect on recurrent stroke[27].
In ADVANCE[28], the combination of indapamide and perindopril in patients with type 2 diabetes (on top of preexisting therapy) for more than 4 years was followed by a significantly greater antihypertensive effect than administration of placebo.
A combination of an ACE inhibitor and a dihydropyridine calcium antagonist was the most widely used combination therapy in Syst-Eur and Syst-China,[29,30] as well as in the HOT study[31] in order to achieve lower BP goals. The combination amlodipine–perindopril was widely used in the ASCOT study, being more effective in lowering BP and cardiovascular events than the combination of a â-blocker with a thiazide[32].
In the ACCOMPLISH (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension) trial[33], more than 11.000 hypertensive patients with a relatively elevated cardiovascular risk were randomized, after stopping previous treatment, to receive benazepril plus either the calcium antagonist amlodipine or hydrochlorothiazide. Over the 3 years of follow-up, both treatments reduced BP very effectively, and the rate of serious side effects was limited and similar between the two groups. In the group receiving the benazepril-amlodipine combination, however, the incidence of the primary endpoint (a composite of several cardiovascular fatal and nonfatal events) was 20% less than in the group receiving the benazepril-hydrochlorothiazide combination, with a significant reduction also in cause-specific events such as myocardial infarction.
In the STAR study[34], hypertensive patients with an impaired fasting glucose exhibited a worse metabolic response to the glucose load test (as well as a greater rate of new-onset diabetes) if treated with a combination of a blocker of the renin–angiotensin system and a diuretic than if treated with the combination of a renin–angiotensin system blocker and a calcium antagonist[59].
The combination of a calcium channel blocker (CCB) and an ACE inhibitor is especially effective because of their comple-

mentary mechanisms. Moreover lower amounts of each component drug are necessary to effectively decrease BP, thereby preventing dose-dependent adverse effects[35], and compound-specific adverse effects can be limited by supporting the physiological actions of the other component. For example, peripheral oedema, a characteristic adverse effect of calcium channel antagonists, is less common when a CCB is administered in combination with an ACE inhibitor or an angiotensin II type-1 receptor antagonist (angiotensin receptor blocker - ARB-)[36-38]. In addition, the combination of an ACE inhibitor and a calcium channel antagonist has synergistic potential in terms of renal, cardiac and vascular effects. The objective of fixed-dose combination antihypertensive therapies is to achieve better BP control in a cost-effective way while minimizing adverse effects[39] (**table 1**).

The lercanidipine/enalapril fixed dose combination

Lercanidipine is a third-generation dihydropyridine calcium channel antagonist that inhibits calcium entry through L-type calcium channels in smooth muscle cells of the cardiovascular system, leading to peripheral vasodilatation and reducing BP[40-42]. It has high lipophilicity, enabling a slower and smoother onset and longer duration of action than other dihydropyridines[43]. Lercanidipine may have antiatherogenic effects beyond BP reduction[40], reducing levels of low-density lipoprotein cholesterol oxidation by 35% in hypertensive patients with diabetes[44], and reducing signs and symptoms of ischaemia, and improves heart function in patients with angina[45]. Lercanidipine has also been reported to have renoprotective effects[46,47], and improves the lipid profile and glucose tolerance[48]. Unlike other dihydropyridine calcium channel antagonists, lercanidipine has renoprotective effects because it induces both afferent and efferent arteriolar vasodilatation[47].

In diabetic patients, lercanidipine treatment led to a significant decrease in glycosylated haemoglobin (HbA1c) level, without negatively affecting glucose omeostasis[49]. In diabetic patients with renal failure, lercanidipine had a good tolerability profile and a neutral effect on plasma lipids, with no impairment in renal function[50]. In hypertensive patients with the metabolic syndrome, lercanidipine appeared to have a better tolerability profile and was associated with fewer vasodilatation-related adverse effects than other

Table 1. Synergistic possibilities with the combination of an angiotensin-converting enzyme inhibitor (ACE-I) and a calcium channel antagonist (CCA)[39].

Effect	DHP-CCA	Non DHP CCA	ACE-I
Renal			
Renal blood flow	↑	↑	↑
Efferent arteriolal tone	Minimal ↓	↓	↓
Afferent arteriolar tone	↓	↓	↓
Proteinuria	Minimal ↓	↓	↓
Renoprotection	No	Possibly	Yes
Vasculature			
Endothelial-mediated vasoconstriction	↓	↓	Minimal effect
Nitric oxide release	No	No	Yes
Arterial compliance	↑	↑	↑
Vascular hypertrophy	↓	↓	↓
Atherogenesis	↓	↓	↓
Cardiac			
Left ventricular hypertrophy	↓	↓	↓
Heart rate	↑	↓	No effect
Left ventricular filling	↑	↑	Minimal effect
Contractility, unloading	Some effect	No effect	Improvement
Coronary flow	↑	↑	Mild ↑
Secondary cardioprotection	No	Some	Yes

ACE= angiotensin-converting enzyme; DHP=dihydropyridine; ↑=increase; ↓=decrease.

dihydropyridine calcium channel antagonists[48]. Enalapril is a prodrug that is hydrolysed to the active form enalaprilat, which decreases plasma levels of angiotensin II by inhibiting ACE, so reducing angiotensin II and leading to peripheral vasodilatation and reduced vascular resistance, decreasing BP values. Enalapril has positive effects on cardiovascular risk factors and prevents decline in renal function[51-53]. A number of clinical trials have demonstrated that the lercanidipine/enalapril combination has better efficacy and tolerability than monotherapy with either agent[54-57]. In addition, lercanidipine was non-inferior to hydrochlorothiazide as add on therapy to enalapril in diabetic patients with hypertension who had not responded to enalapril alone. The fixed-dose formulation of lercanidipine/enalapril was well tolerated in all clinical trials, with an adverse effect rate similar to the component drugs as monotherapy[54-57] and showing to effectively decrease BP.

Conclusions

Calcium channel antagonists are associated with reductions in cardiovascular morbidity and mortality; ACE inhibitors lead to a reduction in myocardial infarction and cardiovascular death. Both these kind of drug appear to diminish CVD above that attributable to BP lowering alone. Based on this evidence, a fixed-dose combination of an ACE inhibitor and a calcium channel antagonist may provide effective cardiovascular protection as it has been shown with the fixed-dose combination of the CCB lercanidipine and the ACE inhibitor enalapril. This combination has greater BP lowering efficacy than either component alone, both in the general hypertensive population and in patients with diabetes. Lercanidipine/enalapril is also well tolerated, with similar adverse effect rates to the component drugs as monotherapy[58]. Moreover the association of a CCB/ACE inhibitor was effective in ameliorating central pressure and not only blood pressure. Anyway, we don't know yet if arterial stiffness and central pressure should become target for therapy or not. TiM

Bibliography

1. **Banegas JR, López-García E, Dallongeville J, *et al.*** Achievement of treatment goals for primary prevention of cardiovascular disease in clinical practice across Europe: the EURIKA study. Eur Heart J 2011:10.1093/eurheartj/ehr080.
2. **Hill MN, Miller NH, Degeest S;** American Society of Hypertension Writing Group. Adherence and persistence with taking medication to control high blood pressure. J Am Soc Hypertens 2011; 5:56-63.
3. **DiMatteo MR, Giordani PJ, Lepper HS, *et al.*** Patient adherence and medical treatment outcomes: a meta-analysis. Med Care 2002; 40:794-811.
4. **Cherry SB, Benner JS, Hussein MA, *et al.*** The clinical and economic burden of nonadherence with antihypertensive and lipid-lowering therapy in hypertensive patients. Value Health 2009; 12:489-497.
5. **Roman MJ, Devereux RB, Kizer JR, *et al.*** Central Pressure More Strongly Relates to Vascular Disease and Outcome Than Does Brachial Pressure: The Strong Heart Study. Hypertension 2007; 50:197-203.
6. **Blood Pressure Lowering Treatment Trialists' Collaboration.** Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet 2003; 362:1527-1535.
7. **Zanchetti A, Hennig M, Hollweck R, *et al.*** Baseline values but not treatment induced changes in carotid intima media thickness predict incident cardiovascular events in treated hypertensives. Findings in the ELSA. Circulation 2009; 120:1084-1090.
8. **Fowkes GF, and the Ankle Brachial Index Collaboration.** Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA 2008; 300:197-200.
9. **De Buyzere M, Clement DL.** Management of hypertension in peripheral arterial disease. Progress Cardiovasc Dis 2008; 50:238-263.
10. **Laurent S, Boutouyrie P, Asmar R, *et al.*** Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension 2001; 37:1236-1241.
11. **Meaume S, Benetos A, Henry OF, *et al.*** Aortic pulse wave velocity predicts cardiovascular mortality in subjects ³70 years of age. Arterioscler Thromb Vasc Biol 2001; 21:2046-2050.
12. **Pannier B, Guerin AP, Marchais SJ, *et al.*** Stiffness of capacitive and conduit arteries: prognostic significance for end-stage renal disease patients. Hypertension 2005;45:592-596.
13. **Hansen TW, Staessen JA, Torp-Pedersen C, *et al.*** Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. Circulation 2006; 113:664-670.
14. **Pauca AL, O'Rourke MF, Kon ND.** Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform. Hypertension 2001; 38:932-937.
15. **The CAFE´ Investigators, for the Anglo-Scandinavian Cardi-**

ac Outcomes Trial (ASCOT) Investigators. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes. Principal results of the Conduit Artery Function Evaluation (CAFE´) Study. Circulation 2006; 113:1213-1225.

16. **Sehestedt T, Jeppesen J, Hansen TW, *et al*.** Which markers of subclinical organ damage to measure in individuals with high normal blood pressure? J Hypertens 2009; 27:1165-1171.
17. **Inoue M, Maeda R, Kawakami H, *et al*.** Aortic pulse wave velocity predicts cardiovascular mortality in middle-aged and elderly Japanese men. Circ J 2009; 73:549-553.
18. **Boutouyrie P, Tropeano AI, Asmar R, *et al*.** Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: a longitudinal study. Hypertension 2002; 39:10-15.
19. **Laurent S, Cockcroft J, Van Bortel L, *et al*.** Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 2006; 27:2588-2605.
20. **Leone N, Ducimetiere P, Gariepy J, *et al*.** Distension of the carotid artery and risk of coronary events: the three-city study. Arterioscler Thromb Vasc Biol 2008; 28:1392-1397.
21. **Williams B, Lacy PS, Thom SM, *et al*.** Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. Circulation 2006; 113:1213-1225
22. **Guerin AP, Blacher J, Pannier B, *et al*.** Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. Circulation 2001; 103:987-992.
23. **Asmar RG, London GM, O'Rourke ME, *et al*.** Improvement in blood pressure, arterial stiffness and wave refl ections with a very-low-dose perindopril/indapamide combination in hypertensive patient: a comparison with atenolol. Hypertension 2001 ; 38:922-926.
24. **de Luca N, Asmar RG, London GM, *et al*.** Selective reduction of cardiac mass and central blood pressure on low-dose combination perindopril/indapamide in hypertensive subjects. J Hypertens 2004, 22:1623-1630.
25. **Wald DS, Law M, Morris JK, *et al*.** Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. Am J Med 2009; 122:290-300.
26. **Mancia G, De Backer G, Dominiczak A, *et al*.** 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2007; 25:1105-1187.
27. **PROGRESS Collaborative Study Group.** Randomised trial of perindopril based blood pressure-lowering regimen among 6108 individuals with previous stroke or transient ischaemic attack. Lancet 2001; 358:1033-1041.
28. **ADVANCE Collaborative Group.** 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.
29. **Staessen JA, Fagard R, Thijs L, *et al*, for The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators.** Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Lancet 1997; 350:757-764.
30. **Liu L, Wang JG, Gong L, *et al*, for the Systolic Hypertension in China (Syst-China) Collaborative Group.** Comparison of active treatment and placebo in older Chinese patients with isolated systolic hypertension. J Hypertens 1998; 16:1823-1829.
31. **Hansson L, Zanchetti A, Carruthers SG, *et al*.** Effects of intensive bloodpressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet 1998; 351:1755-1762.
32. **Dahlöf B, Sever PS, Poulter NR, *et al*, ASCOT Investigators.** Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomized controlled trial. Lancet 2005; 366:895-906.
33. **Jamerson K, Weber MA, Bakris GL, *et al*, ACCOMPLISH Trial Investigators.** Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med 2008; 359:2417-2428.
34. **Bakris G, Molitch M, Hewkin A, *et al*, STAR Investigators.** Differences in glucose tolerance between fixed-dose antihypertensive drug combinations in people with metabolic syndrome. Diabetes Care 2006; 29:2592-2597.
35. **Morgan TO, Anderson A, Jones E.** Comparison and interaction of low dose felodipine and enalapril in the treatment of essential hypertension in elderly subjects. Am J Hypertens 1992; 5 (4 Pt 1): 238-243.
36. **Epstein M.** The benefits of ACE inhibitors and calcium antagonists in slowing progressive renal failure: focus on fixed-dose combination antihypertensive therapy. Ren Fail 1996; 18:813-832.
37. **Kuschnir E, Acuna E, Sevilla D, *et al*.** Treatment of patients with essential hypertension: amlodipine 5mg/benazepril 20 mg compared with amlodipine 5 mg, benazepril 20 mg, and placebo. Clin Ther 1996; 18:1213-1224.
38. **Sanford M, Keam S.** Olmesartan medoxomil/amlodipine. Drugs 2009; 69:717-729.
39. **Borghi C, Cicero AF.** Rationale for the use of a fixed-dose combination in the management of hypertension: efficacy and tolerability of lercanidipine/enalapril. Clin Drug Investig 2010; 30:843-854.
40. **Otero M.** Manidipine-delapril combination in the management of

hypertension. Vasc Health Risk Management 2007; 3:255-263.

41. **Bang LM, Chapman TM, Goa KL.** Lercanidipine: a review of its efficacy in the management of hypertension. Drugs 2003; 63:2449-2472.
42. **McClellan KJ, Jarvis B.** Lercanidipine: a review of its use in hypertension. Drugs 2000; 60:1123-1140.
43. **Meredith PA.** Lercanidipine: a novel lipophilic dihydropyridine calcium antagonist with long duration of action and high vascular selectivity. Expert Opin Investig Drugs 1999; 8:1043-1062.
44. **Rachmani R, Levi Z, Zadok BS, *et al*.** Losartan and lercanidipine attenuate low-density lipoprotein oxidation in patients with hypertension and type 2 diabetes mellitus: a randomized, prospective crossover study. Clin Pharmacol Therap 2002; 72:302-307.
45. **Acanfora D, Gheorghiade M, Trojano L, *et al*.** A randomized, double-blind comparison of lercanidipine 10 and 20 mg in patients with stable effort angina: clinical evaluation of cardiac function by ambulatory ventricular scintigraphic monitoring. Am J Therap 2004; 11:423-432.
46. **Dalla Vestra M, Pozza G, Mosca A, *et al*.** Effect of lercanidipine compared with ramipril on albumin excretion rate in hypertensive type 2 diabetic patients with microalbuminuria: DIAL study (Diabete, Ipertensione, Albuminuria, Lercanidipina). Diabetes, Nutrition & Metabolism - Clin Experiment 2004; 17:259-266.
47. **Robles NR, Ocon J, Gomez CF, *et al*.** Lercanidipine in patients with chronic renal failure: the ZAFRA study. Ren Fail 2005; 27:73-80.
48. **Barrios V, Escobar C, de la Figuera M, *et al*.** High doses of lercanidipine are better tolerated than other dihydropyridines in hypertensive patients with metabolic syndrome: results from the TOLERANCE study. Int J Clin Pract 2008; 62:723-728.
49. **Viviani GL.** Lercanidipine in type II diabetic patients with mild to moderate arterial hypertension. J Cardiovasc Pharmacol 2002; 40:133-139.
50. **Robles NR, Pastor L, Manjon M, *et al*.** Lercanidipine in diabetic patients with renal failure. Nefrologia 2004; 24:338-343.
51. **Ravid M, Brosh D, Levi Z, *et al*.** Use of enalapril to attenuate decline in renal function in normotensive, normoalbuminuric patients with type 2 diabetes mellitus: a randomized, controlled trial. Ann Int Med 1998; 128 (12 Pt 1):982-988.
52. **Rosei EA, Rizzoni D, Muiesan ML, *et al*.** Effects of candesartan cilexetil and enalapril on inflammatory markers of atherosclerosis in hypertensive patients with noninsulin-dependent diabetes mellitus. J Hypertens 2005; 23:435-444.
53. **Hosomi N, Mizushige K, Ohyama H, *et al*.** Angiotensinconverting enzyme inhibition with enalapril slows progressive intima-media thickening of the common carotid artery in patients with noninsulin-dependent diabetes mellitus. Stroke 2001; 32:1539-1345.
54. **Minai K, Matsumoto T, Horie H, *et al*.** Bradykinin stimulates the release of tissue plasminogen activator in human coronary circulation: effects of angiotensin-converting enzyme inhibitors. J Am Coll Cardiol 2001; 37:1565-1570.
55. **Agrawal R, Marx A, Haller H.** Efficacy and safety of lercanidipine versus hydrochlorothiazide as add-on to enalapril in diabetic populations with uncontrolled hypertension. J Hypertens 2006; 24:185-192.
56. **Data on file, Recordati SpA.** Efficacy and tolerability of a combination of lercanidipine and enalapril in patients with mild to moderate essential hypertension not adequately controlled by enalapril treatment (add-on to enalapril) [CLP1-0018] [CLP1-0019]. Milan: 2004.
57. **Puig JG, Calvo C, Luurila O, *et al*.** Lercanidipine, enalapril and their combination in the treatment of elderly hypertensive patients: placebo-controlled, randomized, crossover study with four ABPM. J Hum Hypertens 2007; 21:917-924.
58. **Hair PI, Scott LJ, Perry CM.** Fixed-dose combination lercanidipine/enalapril. Drugs 2007; 67:95-106
59. **Mancia G, Laurent S, Agabiti-Rosei E, *et al*.** Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. J Hypertension 2009; 27:2121-2158.
60. **Ghiadoni L, Bruno RM, Stea F, *et al*.** Central Blood Pressure, Arterial Stiffness, and Wave Reflection: New Targets of Treatment in Essential Hypertension. Current Hypertension Reports 2009, 11:190-196.
61. **Blacher J, Asmar R, Djane S, *et al*.** Aortic Pulse Wave Velocity as a Marker of Cardiovascular Risk in Hypertensive Patients. Hypertension 1999; 33:1111-1117.
62. **Sutton-Tyrrell K, Najjar SS, Boudreau RM, *et al*, for the Health ABC Study.** Elevated Aortic Pulse Wave Velocity, a Marker of Arterial Stiffness, Predicts Cardiovascular Events in Well-Functioning Older Adults Circulation 2005; 111:3384-3390.
63. **Vrijens B, Vincze G, Kristano P, *et al*.** Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. BMJ 2008; 336:1114-1117.

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