RAS Blockade for Every Diabetic Patient: Pro and Con

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The first part of this manuscript offers an overview of clinical data supporting the use of renin-angiotensin system (RAS) inhibitors in every patient with type 1 or type 2 diabetes, based on the known role of the RAS in blood pressure regulation and organ protection. In the second part, a possible, relevant role of drugs other than RAS-active compounds in treating hypertension and preventing cardiovascular disease in type 2 diabetic patients is underlined, paying particular attention to calcium-channel blockers, either alone or, better, in combination with ACE inhibitors.

PRO ARGUMENT—The guidelines of the European Society of Hypertension and the European Society of Cardiology recognize that the first monotherapy to be given to a diabetic patient with elevated blood pressure is an RAS suppressor, either an ACE inhibitor or an angiotensin receptor blocker (ARB) when micro- or macroalbuminuria are present (1). They also recognize that in order to lower blood pressure, all effective and well tolerated drugs can be used. Having admitted the possibility of non-RAS suppression therapies as first line, the guidelines continue by saying that the great majority of diabetic patients will sooner or later present hypertension and that most of them will require combination therapy. In this case, they specify that a blocker of the RAS should be a regular component of the combination and the one preferred when monotherapy is sufficient. In summary, an RAS blocker should be used when an elevation of blood pressure, even within the high normal range, is detected.

The recent reappraisal of European Society of Hypertension Guidelines (2) confirms that initiation of therapy in the high normal range is reserved for diabetic patients with some degree of target organ damage (TOD), in particular microalbuminuria.

Are the guidelines wrong? Probably not, because RAS suppression has three different aspects:

1) Capacity to control blood pressure alone or in combination
2) Capacity to prevent and/or regress TOD
3) Capacity to protect patients with high global cardiovascular risk

I will briefly analyze these three aspects that have led the European Society of Hypertension and the European Society of Cardiology to consider that every diabetic patient deserves to be treated with an ACE inhibitor or an ARB.

Capacity to control blood pressure alone or in combination

RAS suppressors have been shown to be good antihypertensive drugs with a capacity to lower blood pressure similar to that of other monotherapies. Particularly in combination with a diuretic and/or a calcium channel blocker, they have shown very positive and early results specifically in the form of fixed combinations as shown by the data of the ACCOMPLISH (Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension) study (3). Other combinations with a β-blocker or an α-blocker are much less frequently used (except when specific combinations for β-blockers are present). So from the point of view of capacity to attain the elected blood pressure goal, there is no reason to consider any other type of therapy as preferential.

Capacity to prevent and regress TOD

The cardiorenal continuum described by Dzau et al. (4) can be subdivided in clinical practice into three stages: the first is that in which we only detect cardiovascular risk factors (in the case of diabetes) in the absence of what characterizes the second and third stages; second is asymptomatic TOD (the most commonly detected in clinical practice are albuminuria, a diminished estimated glomerular filtration rate, and the presence of electrocardiogram alterations compatible with left ventricular hypertrophy [LVH]); and the third is symptomatic TOD or overt cardiovascular disease.

The finding of TOD represents an advanced stage in the cardiorenal continuum predicting that the time to initiation of symptomatic TOD or overt disease is nearer than compared with the previous stage.

In diabetic patients, renal protection includes prevention of new onset microalbuminuria, which has been shown to be dependent on the combination of blood pressure control and RAS suppression by the BENEDICT (Bergamo Nephrologic Diabetes Complications Trial) and the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) studies (5,6). The latter study also proved that these two objectives ensure a decrease or even a normalization of albuminuria and a decrease in the progression of advanced diabetic nephropathy (6,7). However, more strict blood pressure control (attaining values <120 mmHg for systolic blood pressure together with RAS suppression and of course other medications) could be partly deleterious for renal function as shown by the ACCORD (Action to

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Control Cardiovascular Risk in Diabetes) study (8).

Diminution of albuminuria with RAS suppressors has been shown to protect the cardiovascular system from future events as shown by the LIFE (Losartan Intervention For Endpoint reduction in hypertension) and RENAAL (Reduction of End Points in Type 2 Diabetes With the Angiotensin II Antagonist Losartan) studies (9,10)

With respect to LVH, this cardiac alteration can be prevented with trandolapril, as shown in the BENEDICT and TRANSCEND (Telmisartan Randomized Assessment Study in ACE Intolerant Patients with Cardiovascular Disease) studies (5,11), and the use of RAS suppressors together with that of calcium channel blockers has been shown to be the best to regress/reduce LVH even to normal ranges (12).

In summary, available data indicate that RAS suppressors are particularly suitable to prevent or regress TOD.

Capacity to protect patients with a high global cardiovascular risk

Diabetic patients are considered to have a level of risk similar to that observed in nondiabetic patients in situations of secondary prevention (13), in which the administration of RAS suppressor is mandatory in order to prevent cardiovascular events and death. This has been shown by the meta-analysis of HOPE (Heart Outcomes Prevention Evaluation), EUROPA (European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease), and PEACE (Prevention of Events with Angiotensin-Converting Enzyme Inhibition) studies (14). The need for an ACE inhibitor or an ARB in diabetic patients cannot only be based on the presence of TOD, in particular albuminuria, but should also include the potential capacity of these drugs to diminish atherothrombotic events. This statement puts an end to the sterile discussion that RAS suppression does not protect renal function in the absence of albuminuria (longer follow-ups are needed to provide further proof) because cardiovascular protection makes the use of these drugs mandatory, independent of renal outcome.

In summary, diabetic patients deserve to be treated either with an ACE inhibitor or an ARB immediately when they are diagnosed, provided blood pressure is in the range of high-normal or above. In cases where symptomatic TOD is present, treatment with an ACE inhibitor or ARB is recommended even if blood pressure is within normal range.

CON ARGUMENT—RAS-active compounds have revolutionized the therapeutic approach to the treatment of hypertension, becoming one of the most innovative classes of drugs discovered over the past 5 decades. However, despite their proven efficacy in slowing the progression of renal damage during the course of both type 1 and type 2 diabetes through their powerful antiproteinuric effect (15–17), some concerns can be raised regarding the compelling indication to their use in every patient with type 1 or type 2 diabetes. These concerns can be summarized in three main points: *1*) the real nephroprotective effect in type 2 diabetic patients with normal albumin excretion rate is still under debate; *2*) trial evidence of superiority in reducing cardiovascular risk when compared with other antihypertensive drugs—such as diuretics or calcium channel blockers—is lacking; and *3*) although RAS blockers are credited with cardioprotective mechanisms other than blood pressure lowering (reduction in angiotensin II–mediated vasoconstriction, thrombosis, salt/water retention, oxidative stress and inflammation, and promotion of vascular remodeling and restructuring [18]) it is uncertain that these ancillary mechanisms add significantly to the reduction of cardiovascular risk in patients with diabetes.

RAS-active compounds and nephroprotection in type 2 diabetes

The only randomized clinical trial documenting efficacy of an ACE inhibitor in the primary prevention of diabetic nephropathy (or, better, its early marker microalbuminuria) in type 2 diabetes is BENEDICT, a placebo-controlled study in which ramipril significantly reduced the incidence of microalbuminuria over a 5-year follow-up (5). So far, this result has not been convincingly replicated using an ARB, as shown by the recent DIRECT (Diabetic Retinopathy Candesartan Trial) study (19). Here, three large cohorts of normoalbuminuric patients with type 1 or type 2 diabetes and different degrees of retinal involvement were randomized to receive candesartan or placebo. Although the primary outcome was progression of retinopathy, incidence of microalbuminuria was also analyzed, and the ARB did not perform better than placebo over a period of 5 years.

RAS-active compounds and reduction of cardiovascular risk

Regarding this second point, it is relevant to recall that one of the most complete meta-analyses so far performed of primary and secondary prevention trials indicates that reduction of blood pressure, in particular systolic pressure, per se can account for the main cardiovascular outcomes (20). Aggregate information from the numerous clinical trials published over the last few years is consistent with the conclusion that the four main classes of drugs—diuretics, RAS-active compounds, calcium channel blockers, and β-blockers—have a substantially identical antihypertensive efficacy. For example, a meta-analysis of 354 randomized trials including more than 40,000 individuals on active treatment and 16,000 on placebo, concluded that a standard dose of any of these drugs induces equivalent response, reducing systolic values by 9.1 mmHg and diastolic values by 5.5 mmHg (21); similarly, no difference in the antihypertensive effect is detected among different drugs in type 2 diabetic individuals, even in head-to-head comparison (22). Thus, in most patients, a standard dose of a RAS-active compound is likely to exert an antihypertensive effect comparable to that of any other antihypertensive agent. In addition, several large, long-term studies carried out over the last 10 years have shown that the different classes of antihypertensive drugs are equally effective in the prevention of mortality or cardiovascular events in type 2 diabetes. The INVEST (International Verapamil-Trandolapril Study) study, including more than 22,500 hypertensive patients with coronary impairment, compared a nondihidropiridinic calcium channel blocker and a β-blocker, with the opportunity to add an ACE inhibitor or a diuretic in order to reach the target. The two treatments achieved similar systolic and diastolic blood pressure plateaus, but there was no difference in the primary end point (all-cause death, nonfatal myocardial infarction, and nonfatal stroke) either in nondiabetic or diabetic patients (23). The IDNT (Irbesartan versus Amlodipine Diabetic Nephropathy Trial) (24), with more than 1,700 patients with hypertension and nephropathy, while documenting a remarkable nephroprotective effect of the ARB, was unable to show superiority of irbesartan in terms of incidence of major cardiovascular events, cardiovascular and total mortality. In the latter study, cardiovascular risk

reduction was not the primary outcome. However, other studies with a cardiovascular primary end point have failed to attain superior cardiovascular protection with RAS-active compounds (25). In TRANSCEND, performed in a large cohort of patients intolerant to ACE inhibitors with cardiovascular disease or diabetes with end-organ damage, telmisartan had no significant effect on the primary outcome (the composite of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure) at the end of a 5-year follow up, despite significantly lower blood pressure values achieved in the treatment group (26).

The cardiovascular effects of a dual blockage of RAS require mention. In the ONTARGET (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) study, the combined use of telmisartan and ramipril was associated with more adverse events in patients with established atherosclerotic vascular disease or with diabetes and end-organ damage (27). In a separate prespecified analysis aimed to test the superiority of this treatment in preventing proteinuria, an adverse effect of combination therapy on typical renal outcomes and on decline of glomerular filtration rate was evident (28). It is well known that the American Heart Association guidelines do not currently recommend the combined use of ACE inhibitors and ARBs.

Another element to consider when starting an antihypertensive therapy should be the ethnicity of the patients. Information from both ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) and LIFE studies (29,30) clearly establish the primacy of diuretic-based over RAS compounds–based therapy in the management of black hypertensive patients without renal disease or heart failure, confirming the lesser benefit of RAS inhibitors in preventing cardiovascular outcomes in this ethnic group. These trials have provided further refinement that guides the use of RAS inhibitors for control of hypertension.

Recently, this nonsuperiority of RAS-active compounds in protecting the heart has been extended to prediabetic states. In the NAVIGATOR (Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research) study in patients with impaired glucose tolerance and established cardiovascular disease or risk factors, valsartan but not nateglinide reduced the incidence of type 2 diabetes but failed to affect the cardiovascular event rate (composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, arterial revascularization, or hospitalization for unstable angina) when compared with placebo (31). Similarly, in DREAM (Diabetes REduction Assessment With ramipril and rosiglitazone Medication) ramipril did not reduce the incidence of the primary end point (death or diabetes onset) in >5,200 patients with impaired fasting glucose or impaired glucose tolerance (32).

Evidence accrued from meta-analyses, however rigorous, may miss important details. For example, one might ask whether the various antihypertensive agents differ in cardioprotection viz cerebrovascular protection. Here, the comprehensive evaluation carried out by the Blood Pressure Lowering Treatment Trialists' Collaboration, may offer helpful clues. In over 33,000 diabetic patients and 125,000 nondiabetic individuals allocated to different antihypertensive drug classes as well as more versus less aggressive therapeutic schemes, the following results were obtained. First, the different drugs are always better than placebo, and the intensive rather than conventional antihypertensive treatment makes the real difference in terms of prognosis. Second, no difference between ACE inhibitors and other classes was detected for major cardiovascular events (33). However, ACE inhibitors and, even more, ARBs were slightly better in reducing risk of coronary artery disease, whereas calcium channel blockers provided significant advantages in terms of cerebrovascular protection. Several years ago, Verdecchia et al. (34) performed a similar meta-analysis of 28 placebo-controlled trials, (180,000 patients) to test whether different drug classes differed for heart or brain protection. The results confirmed a better efficacy of ACE inhibitors in preventing myocardial infarction and superiority of calcium channel blockers in preventing stroke, irrespective of the attained blood pressure values. More recently, these observations have been supported by a huge meta-analysis including almost half a million patients in three categories: no personal history of cardiovascular disease, history of cardiovascular disease, and personal history of stroke. All drug classes showed the same efficacy in reducing cardiovascular disease for any given level of blood pressure reduction; the only compounds showing a small addictive effect were, as expected, β-blockers in the 3 months immediately following an acute myocardial infarction, and calcium channel blockers in the prevention of stroke. Neither the pretreatment of blood pressure nor the preexistence of cardiovascular disease seemed to play any role. The higher the blood pressure, the better the drug effect with the effect of age being marginal (35).

Obviously, such clues as are derived from the compilation of heterogeneous material cannot constitute indications; nevertheless, they may help the therapeutic choice in the individual patient with a specific phenotype (e.g., with a strong family history of stroke).

The real role of the "ancillary mechanisms"

It is relevant to try to point out the real weight of ancillary mechanisms, for example the anti-inflammatory effects exerted by RAS-active drugs, in preventing macrovascular complications in type 2 diabetes. Several observations performed in cell and animal models have documented relevant anti-inflammatory and antiproliferative properties of RAS-active compounds (36) that have the potential to improve myocardial function and performance (37) and vascular dispensability by reducing arterial stiffness (38). In theory, all these mechanisms should translate into cardiovascular benefit in the patient with diabetes; however, clinical trial evidence for a material role of the so-called "pleiotropic effects" is, at present, scanty, given that in the presence of comparable blood pressure levels, RAS-active drugs do not seem to offer any supplementary cardiovascular protection.

One might object that it is very difficult to reach an adequate blood pressure control in type 2 diabetic patients using just one compound: combination therapy is often required from the very beginning. From this perspective, a RAS-active drug should definitely be used, especially for its nephroprotective effect. This is definitely true, but the clinical complexity of diabetes should favor specific associations. For example, several clinical trials have shown that calcium channel/RAS blockade combinations provide greater blood pressure reductions and improve renal function and metabolic outcomes in patients with diabetic and nondiabetic kidney disease early and to a greater extent than diuretic-based combinations (39), presumably also by increasing arterial compliance, arterial dispensability, and flow-mediated vasodilation.

In conclusion, improvement in blood pressure control in patients with type 2 diabetes and hypertension is associated with a definite, clinically relevant reduction in risk of micro- and macrovascular disease. RAS-active compounds clearly provide better nephroprotection than other antihypertensive agents, but they may be equal in terms of cardioprotection. Irrespective of the drug class, an optimal blood pressure control often requires the use of several compounds, if the benefits are to be sustained.

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References

1. Mancia G, De Backer G, Dominiczak A, et al.; Management of Arterial Hypertension of the European Society of Hypertension; European Society of Cardiology. 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
2. Mancia G, Laurent S, Agabiti-Rosei E, et al.; European Society of Hypertension. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. J Hypertens 2009;27:2121–2158
3. 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
4. Dzau VJ, Antman EM, Black HR, et al. The cardiovascular disease continuum validated: clinical evidence of improved patient outcomes: part II: Clinical trial evidence (acute coronary syndromes through renal disease) and future directions. Circulation 2006;114:2871–2891
5. Ruggenenti P, Fassi A, Ilieva AP, et al.; Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) Investigators. Preventing microalbuminuria in type 2 diabetes. N Engl J Med 2004;351:1941–1951
6. Ninomiya T, Perkovic V, de Galan BE, et al.; ADVANCE Collaborative Group. Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. J Am Soc Nephrol 2009;20:1813–1821
7. Lambers Heerspink HJ, Ninomiya T, Perkovic V, et al.; ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide in patients with type 2 diabetes and chronic kidney disease. Eur Heart J 2010;31:2888–2896
8. Ginsberg HN, Elam MB, Lovato LC, et al.; ACCORD Study Group. Effects of intensive blood pressure control in type 2 diabetes mellitus. N Engl J Med 2010;362:1563–1574
9. Ibsen H, Olsen MH, Wachtell K, Borch-Johnsen K, Lindholm LH, Mogensen CE. Reduction in albuminuria translates to reduction in cardiovascular events in hypertensive patients with left ventricular hypertrophy and diabetes. J Nephrol 2008;21:566–569
10. de Zeeuw D, Remuzzi G, Parving HH, et al. Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. Circulation 2004;110:921–927
11. Mann JF, Schmieder RE, Dyal L, et al.; TRANSCEND (Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease) Investigators. Effect of telmisartan on renal outcomes: a randomized trial. Ann Intern Med 2009;151:1–10, W1-2
12. Klingbeil AU, Schneider M, Martus P, Messerli FH, Schmieder RE. A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension. Am J Med 2003;115:41–46
13. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229–234
14. Dagenais GR, Pogue J, Fox K, Simoons ML, Yusuf S. Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. Lancet 2006;368:581–588
15. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD; The Collaborative Study Group. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. N Engl J Med 1993;329:1456–1462
16. Wilmer WA, Hebert LA, Lewis EJ, et al. Remission of nephrotic syndrome in type 1 diabetes: long-term follow-up of patients in the Captopril Study. Am J Kidney Dis 1999;34:308–314
17. Parving HH, Lehnert H, Bröchner-Mortensen J, Gomis R, Andersen S, Arner P; Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001;345:870–878
18. Jankowski P, Safar ME, Benetos A. Pleiotropic effects of drugs inhibiting the renin-angiotensin-aldosterone system. Curr Pharm Des 2009;15:571–584
19. Bilous R, Chaturvedi N, Sjølie AK, Fuller J, Klein R, Orchard T, Porta M, Parving HH. Effect of candesartan on microalbuminuria and albumin excretion rate in diabetes: three randomized trials. Ann Intern Med 2009;151:11–20
20. Staessen JA, Li Y, Thijs L, Wang JG. Blood pressure reduction and cardiovascular prevention: an update including the 2003-2004 secondary prevention trials. Hypertens Res 2005;28:385–407
21. Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. BMJ 2003;326:1427
22. Whelton PK, Barzilay J, Cushman WC, et al.; ALLHAT Collaborative Research Group. Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Arch Intern Med 2005;165:1401–1409
23. Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al.; INVEST Investigators. A calcium antagonist vs. a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. JAMA 2003;290:2805–2816
24. Lewis EJ, Hunsicker LG, Clarke WR, et al.; Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851–860
25. Julius S, Kjeldsen SE, Weber M, et al.; VALUE trial group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet 2004;363:2022–2031
26. Yusuf S, Teo K, Anderson C, et al.; Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. Lancet 2008;372:1174–1183
27. Yusuf S, Teo KK, Pogue J, et al.; ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008;358:1547–1559
28. Mann JF, Schmieder RE, McQueen M, et al.; ONTARGET investigators. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. Lancet 2008;372:547–553
29. Wright JT Jr, Dunn JK, Cutler JA, et al.; ALLHAT Collaborative Research Group. Outcomes in hypertensive black and nonblack patients treated with chlorthalidone,

amlodipine, and lisinopril. JAMA 2005; 293:1595–1608
30. Julius S, Alderman MH, Beevers G, et al. Cardiovascular risk reduction in hypertensive black patients with left ventricular hypertrophy: the LIFE study. J Am Coll Cardiol 2004;43:1047–1055
31. McMurray JJ, Holman RR, Haffner SM, et al.; NAVIGATOR Study Group. Effect of valsartan on the incidence of diabetes and cardiovascular events. N Engl J Med 2010;362:1477–1490
32. Bosch J, Yusuf S, Gerstein HC, et al.; DREAM Trial Investigators. Effect of ramipril on the incidence of diabetes. N Engl J Med 2006;355:1551–1562
33. Turnbull F, Neal B, Algert C, et al.; Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. Arch Intern Med 2005; 165:1410–1419
34. Verdecchia P, Reboldi G, Angeli F, et al. Angiotensin-converting enzyme inhibitors and calcium channel blockers for coronary heart disease and stroke prevention. Hypertension 2005;46:386–392
35. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 2009;338: b1665
36. Sironi L, Nobili E, Gianella A, Gelosa P, Tremoli E. Anti-inflammatory properties of drugs acting on the renin-angiotensin system. Drugs Today (Barc) 2005;41: 609–622
37. Helmig S, Schuckenböhmer P, Heger J, Euler G, Piper HM, Schlüter KD. Direct effects of the angiotensin-converting enzyme inhibitor ramiprilat on adult rat ventricular cardiomyocytes. Acta Physiol (Oxf) 2007;191:267–274
38. Tropeano AI, Boutouyrie P, Pannier B, et al. Brachial pressure-independent reduction in carotid stiffness after long-term angiotensin-converting enzyme inhibition in diabetic hypertensives. Hypertension 2006;48:80–86
39. Reboldi G, Gentile G, Angeli F, Verdecchia P. Exploring the optimal combination therapy in hypertensive patients with diabetes mellitus. Expert Rev Cardiovasc Ther 2009; 7:1349–1361