Review Article

Monotherapy versus Polytherapy in Patients with Hypertension

Auslin Sam, Blessy Merin Thankachan, Kameswaran R*, Sambathkumar R.
Department of Pharmacy Practice, J.K.K. Nattraja College of Pharmacy, Kumarapalayam, Tamil Nadu, India.
***Corresponding author's E-mail:** kameswaran.r@jkkn.org

Received: 07-11-2017; **Revised:** 28-11-2017; **Accepted:** 13-12-2017.

ABSTRACT

Hypertension is a long term medical condition that is defined by the raise in blood pressure in the arteries. It can strain the heart and cause various multi system disorders. It is one of the risk factor for causing stroke, renal failure, myocardial infraction, congestive cardiac failure and other such diseases. There is plenty of co-relation of various diseases with Hypertension. Treatment of Hypertension deals with the control of blood pressure as well as preventing it comorbidities. It should help improve the quality of life of the patient. Even though an initial mono therapy is used to treat hypertension it is soon changed to poly therapy. Combination therapy is proved to be more effective in reducing morbidity and mortality.

Keywords: Hypertension, Mono therapy, poly treatment.

INTRODUCTION

Hypertension is a prevalent cardiovascular disease which is a major reason for mortality and morbidity. It is one of the main cause of other cardiovascular disease and a leading cause for a number of deaths worldwide. [1] According to a report by the American Heart Association based on 2007-2010 data, 33.0% of US adult's ≥ 20 years of age were in hypertension. [2] Hypertension (systolic pressure > 140 mmHg or diastolic pressure > 90 mmHg) is a risk factor for stroke, myocardial infarction, renal failure, congestive heart failure and peripheral artery disease. There is a classified association between blood pressure and the risk of cardiovascular disease. [3, 4] obtaining the target blood pressure level by mono therapy can be challenging currently, especially for the patients who are suffering from other diseases. It is demonstrated that a majority of hypertensive patients need two or more antihypertensive drugs are needed to lower their blood pressure effectually. Consequently, fixed-dose which can be defined as that several active agents that are combined in single pharmaceutical formulation appears to be a novel and has power in overcoming the cardiovascular disease.

As a repercussion of the advanced alertness of the damage caused by hypertension and with the perception that the development of hypertension induced cardiovascular diseases, cerebrovascular and Reno vascular diseases can be slowed, if not stopped by its treatment. [5] A few prospects of initial combination treatment have been expected: Two drugs can be given at low doses so decreasing the risk of adverse effects. Combination therapy caters to more rapid control of blood pressure than mono therapy. Adherence is also increased. [4]

Need for combination therapy

BP is determined by three factors: renal sodium excretion and resultant plasma and total body volume, cardiac performance, and vascular tone. These aspects regulate intravascular volume, cardiac output, and systemic vascular resistance, which are the instantaneous hemodynamic elements of Blood pressure. Both the sympathetic nervous system and the (RAAS) (renin-angiotensin-aldosterone system) are involved in modifying these limitson a real-time basis. In addition to this genetic makeup, diet, and environmental factors influence blood pressure in patients. [6]

Combination therapy is categorized into two types: one is several drug prescribed separately; the other is drugs in fixed-dose combinations. Undoubtedly, the prior brought much distress for the patients particularly the elders who were tired of taking a series of pills every day. [7] Recent clinical trials suggest that the approach of using mono therapy for the control of hypertension is not likely to be effective in most patients and especially in those with some comorbidities (e.g. DM, heart failure). The achievements of BP goal typically require two or more medications in various settings. [8-12] The importance of blocking multiple physiological pathways is highlighted by studies using a treatment policy known as "sequential mono therapy". This method is based on the inspection that BP response to different antihypertensive medications is often variable, and BP control should be more easily accomplished with mono therapy if patients are exposed to multiple drugs and then treated with the most operative agent. [13] Using combination therapy for initial management helps to achieve the target blood pressure with fewer adverse effects since lower doses of the agent is used. [14-16] Potential economic advantages include a decreased need to change medications and improved long-term outcomes secondary to improved blood pressure control. [17] Initial management with

combination therapy should be considered in any patient whose blood pressure is greater than 20 mm Hg above systolic goal or 10 mm Hg above diastolic goal. [18, 19]

Considerations for Combinations

Effectiveness

Combination therapy is decided based on the cautiousco-administration of two or more antihypertensive agents. Combining two drugs results in partial or complete addition of their BP-lowering effects. Additive combinations are more effective in blood pressure reduction. [20- 22]

Acceptability

Improving the acceptability of treatment is a key component in deciding rational drug combinations. This effect will occur whenever side effects associated with a particular agent are nullifiedby the pharmacologic properties of an added drug. [22] Most antihypertensive agents lead to dose-dependent side effects; high dose of mono therapy may lead to adverse effects. In such a situation, a decreased dose of the initial agent in combination with another anti -hypertensive may be given in order to decrease dose dependent side effects even if no additional BP reduction is achieved. [23]

Adherence

Drug combinations have established an increase in patient adherence. It increases adherence by decreasing the number of drugs and dosing frequency moreover it has resulted in a reduction of adverse effects which resulted in patients preferring combination drugs.

Common combinations

There are several common drug classes can be used in hypertension: thiazide diuretics, calcium channel blockers (CCB's), beta (b)-blockers, alpha (a)-blockers, ACEI, ARB and some centrally acting drugs.

Thiazide diuretics plus ACEI/ARB

Low-dose thiazide-type diuretic with an ACE inhibitor, ARB, or directrenin inhibitor results in BP reduction. [24] This combination will result in thediuretic-induced increase in plasma renin activity. The salt loss will increase the antihypertensive effect of RAAS blocker. An ARB will alsomitigate the metabolic effects of thiazide diuretics like hypokalemia and hyperglycemia. Studies have showed that antihypertensive effectiveness of this combination in low doses, produces substantially greater reductions in BP and higherresponse rates than either of the treatments alone.[24,25] When elderly patients treated with just an ACEI fail to achieve idealblood pressure, fixed-dose combinations consisting of thiazide diuretics and ACEI can lower the BP.By the inhibition of ARB on angiotensin II, the antihypertensive effect of thiazide diuretics was increased greatly moreover ARBalso helps in decreasing potassium loss and hyperuricemia causedby thiazide diuretics resulting the interdiction of aldosterone secretion. [26-27]

Thiazide diuretics plus b-blockers

The combinations of diuretics and b-blockers have found to significantly reduce the side effects of Thiazide diuretic mono therapy such as volume depletion and total body sodium loss. [28-30] The antihypertensive effects of b-blockers are interceded through the decrease in the cardiac output and suppression of renin release. [31] These combinations are classified astolerable, understanding that their use is related with increased risk of glucose intolerance, fatigue, and sexual dysfunction. [32]

B-blockers plus CCB's

CCB or commonly known as calcium channel inhibitors is an important class of antihypertensive agents that inhibit voltage dependent calcium channels which relax vascular smooth muscles and decrease peripheral resistance, such that the BP decreases. The two types of calcium channel blockers are: dihydropyridine and non-dihydropyridine. It is testified that the non dihydropyridine CCB's including verapamil and diltiazem cannot be combined with b-blockers because of the manifestation of symptomatic bradycardia and atrio-ventricular block. However, the combination of b-blockers and dihydropyridine CCB's can be ideal. The control of renin level due to b-blockers will emphasizes the vasodilator properties, thereby achieving synergistic antihypertensive effects. [33] In a study, low-dose combination of felodipine and metoprolol produced BP decline comparable to maximum doses of each agent with an incidence of edema similar to placebo. [34, 35]

B-blockers plus ACEI/ARB

These drug classes are both cardio-protective and are commonlyco-administered to patients with coronary heart disease or heart failure. Trials have proved that adding a b-blocker to an ACEI did not offer superiority in lowering blood pressure than single therapy with ACEI. [36] Literature has also reported that combinations of renin-angiotensin-aldosterone system blockers and beta-blockers provided very little additional antihypertensive effects compared with the single therapy. [37]

CCB's plus ACEI/ARB

ACEI and ARB inhibit the renin-angiotensin-aldosterone system (RAAS). Calcium channel blockers as antihypertensive agents that will increase the sensitivity to the renin angiotensin-aldosterone system (RAAS) and lead to an enhancement of renin state, which will increase the antihypertensive effects of ACEI/ARB. The combination of an ACE inhibitor or ARB with a CCB results in synergistic BP reduction. [38-40] Addition of any of the two RAAS inhibitors enhances the tolerability of the CCB. Due to their anti-sympathetic effects, RAAS inhibitors dulled the increase in heart rate that may accompany treatment with a dihydropyridine- type CCB. RAAS inhibitors partially nullified the peripheral edema, which is a dose-limiting side effect of CCBs. [41] ACE

inhibitor/CCB combination lowered the combined end point of cardiovascular death, myocardial infarction, and stroke by 20% compared with the ACE inhibitor/diuretic combination. [42] Previous study on the fixed-dose combinations of lercanidipine plus enalapril revealed that this combination provided renal protection for patients with chronic renal failure. [43]

Thiazide Diuretics + Potassium-sparing Diuretics

Hypokalemia is an exceptionally criticaldose-related side effect of thiazide diuretics. By decreasing hypokalemia, the combination of hydrochlorothiazide (HCTZ) with a potassium-sparing diuretic such as triamterene, amiloride, or spironolactone expands its safety profile. [44-45]

Latest data proving the importance of aldosterone blockade in obese patients and the efficacy of aldosterone blockade in aiding the accomplishment of BP goals, the spironolactone/HCTZ combination is particularly well-suited in such individuals. [46]

Special considerations

Diabetes and Proteinuria

Hypertension with diabetes may increase the risk of both macro vascular and micro vascular complications of diabetes. [47] Certain trails have shown decrease in these complications when blood pressure was lowered to safer limits (< 130/80 mm of Hg). Achieving this blood pressure control though mono-therapy was found to be difficult. [48] RAAS inhibitors, CCBs, b-blockers and diuretics maybe used to treat hypertension in patients with DM although the most favored combination is one that inhibits the RAAS and second choice might be CCBs, ACEIs, ARB and diuretics. The results have constantly shown a beneficial renal protective effect of ACEIs and ARBs in diabetic nephropathy. The combined therapy with an ARB and a CCB is useful in anti proteinuric effect in patients with type 2 diabetic nephropathy, even when their renal function is reduced. [49]

Dyslipidemia and Hypertension

Hypertension and hypercholesterolemia are risk factors for heart disease, these two together cause an intensification in coronary heart disease related events. [50] Telmisartan has an exceptional property that stimulates peroxisome proliferator-activated receptor-γ (PPAR γ) and is proposed to improve insulin sensitivity and reduce triglyceride levels, leading to a reduction of the risk for atherosclerosis. Telmisartan may speed up reversal of cholesterol transport or inhibit net cholesterol absorption through activation of ABC1, leading to lowering of TC and low density lipids cholesterol. [51] These results suggest that telmisartan may have the capability to lower cholesterol levels. Thus using a telmisartan alone or in combination with a diuretic/CCB can be useful in patients with dyslipidemia. [52]

Heart failure with Hypertension

JNC-7 guidelines recommend diuretics, beta blockers, ACE inhibitors, ARBs, and aldosterone antagonists in the treatment of hypertension in patients with heart failure. [18] Those medications have proved to reduce morbidity and mortality in patients with heart failure. It is revealed that aldosterone antagonists are beneficial in the treatment of heart failure ranging from moderate to severe. Hyperkalemia may be caused by combination of ACE inhibitors, ARBs, and aldosterone antagonists hence it is contraindicated in patients with heart failure. ACE inhibitors can be substituted by ARBs in patients who can't tolerate ACE inhibitors. The choice of agents is based on severity of heart failure, left ventricular ejection fraction, and history of myocardial infarction. [53]

Chronic renal failure with Hypertension

Monotherapy is not idealas it doesn't lower the level of blood pressure required to slow the decline in glomerular filtration rate. Combination therapy often aids the renal failure patients by lowering their blood pressure. [54] ACE inhibitor or ARB along with a diuretic or CCBs is the first line drug for a protein uric kidney disease. [55, 56] A decline in urinary albumin excretion was noticed with ACEI and an ARB than with monotherapy in those patients preferred by diabetic nephropathy. It is also noticed that these combinations may result in the increase in serum potassium concentrations and deterioration of renal anemia. [57-60] Those patients with hypertension and non-diabetic proteinuric kidney a combination of CCBs with ACE inhibitors have accomplished greater reduction in blood pressure but did not decrease the progression of end stage renal disease. [61]

Hypertension in thyroid disorders

Hypertension is a frequent association with hyperthyroidism with an estimated prevalence of 20%-30%. The exact mechanism by which the BP is increased is not known however it might be due to the hastening of structural changes in the vascular tissue by the thyroid deficiency and the variationin autonomic nervous function which leads to the hemodynamic changes. In those patients with thyrotoxicosis it is observed that the systolic pressure is elevated and the diastolic pressure is low. [56]

Hypertension in Pregnancy and Breast feeding

Hypertension complicates 5% to 7% of all pregnancies. Preeclampsia, characterized by onset Hypertension, proteinuria, and multisystem involvement, is responsible for substantial maternal and fetal morbidity and is a marker for future cardiac and metabolic disease.

Drugs preferred during the pregnancy are:

Ist line - Methyl dopa, Beta blocker (propranolol) andLabetalol

IInd line - Metoprolol, atenolol and Calcium channelblocker (nifedipine)

III[rd] line agents-clonidine, diuretics

CONCLUSION

Hypertension is a disease that brings about various changes in the cardiac and vascular function. In order to keep the blood pressure under complete control a combination therapy should be incorporated in the regimen. Paramount effectiveness and decreased side effects is the important quality when it comes to selection of a combined therapy. It is seen that combination drug improves tolerability and adherence as well. It is seen that most of the current guidelines suggest a combination of drugs in order to improve the quality of life of the patient. The treatment should also improve the mortality and morbidity rates. The choice of the combination of drug depends on the various risk factors and co morbidities like renal disease, diabetics, patient factors and the various adverse effects of the drug.

REFERENCE

1. Chow CK, TeoKK, Rangarajan S, Islam S, Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high, middle, and low-income countries, *Journal of American Medical Association*, 310, 2013, 959-996.
2. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Heart disease and stroke statistics a 2013 update, *Circulation,* 127, 2013, 236-245.
3. Yoder SR, Thornburg LL, Bisognano JD, Hypertension in pregnancy and women of childbearing age**,** *American Journal of Medicine,* 122, 2009, 890-895.
4. Mancia G, De Backer G, Dominiczak A, Cifkova R, Guidelines for themanagement of arterial hypertension: The Task Force forthe Management of Arterial Hypertension of the EuropeanSociety of Hypertension (ESH) and of the European Societyof Cardiology (ESC), *Journal of Hypertension,* 28, 2007, 1462–1536.
5. Yusuf S, Pogue J, Bosch J, Effects of an angiotensin converting enzyme inhibitor, ramipril, on death from cardiovascular causes, myocardial infarction and stroke in high risk patients , *New England Journal of Medicine*, 342, 2000, 145-153.
6. Sarafidis PA, Khosla N, Bakris GL, Antihypertensive therapy in the presence of proteinuria, *American Journal of Kidney Disease*, 49, 2007, 12-26.
7. Reasner C, Olansky L, Seck TL, Williams-Herman DE, The effect of initial therapy with the fixed-dose combination of sitagliptin and metformin compared with metformin monotherapy in patients with type 2 diabetes mellitus, *Diabetes Obesity and Metabolism*, 13, 2011, 644-652.
8. M C Dunlay , V Fitzpatrick , S Chrysant , E A Francischetti, Losartan potassium as initial therapy in patients with severe hypertension, *Journal of Human Hypertension,* 9, 1995, 861-867.
9. Oparil S, Ripley E, Candesartan cilexetil enhances blood pressure reduction severe (state 3, JNC-VI) hypertensive patients inadequately controlled with HCTZ, *American Journal of Hypertension,* 11, 1998, 121A.
10. Larochelle P, Flack JM, Marbury TC, Sareli P, Effects and tolerability of irbesartan versus enalapril in patients with severe hypertension, *American Journal of Cardiology,* 80, 1997, 1613-1615.
11. Cifkova R, Peleska J, Hradec J, Pinterova E, Valsartan and atenolol in patients with severe essential hypertension, *Journal of Human Hypertension,* 12, 1998, 563-567.
12. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial, *Lancet,* 351, 1998, 1755-1762.
13. Dickerson JE, Hingorani AD Ashby MJ, Palmer CR, Optimisation of antihypertensive treatment by crossover rotation of four major classes, *Lancet*, 353, 1999, 2008–2013.
14. Giles TD, Rationale for combination therapy as initial treatment for hypertension, *Journal of Clinical Hypertension,* 5, 2003, 4-11.
15. Elliott WJ, Is fixed combination therapy appropriate for initial hypertension treatment? *Current Hypertension Report*, 4, 2002, 278-285.
16. Ruilope LM, Malacco E, Khder Y, Kandra A, Efficacy and tolerability of combination therapy with valsartan plus hydrochlorothiazide compared with amlodipine monotherapy in hypertensive patients with other cardiovascular risk factors: the VAST study, *ClinicalTherapeutics*, 27, 2005, 578-587.
17. Ambrosioni E, Pharmacoeconomics of hypertension management: the place of combination therapy, *Pharmacoeconomics*, 19, 2001, 337-347.
18. Chobanian AV, Bakris GL, Black HR, Cushman WC, Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, *Hypertension*, 42, 2003, 1206-1252.
19. Bakris GL, Weir MR, Black HR, Improving blood pressure control rates: is there more we can do? *Journal of Clinical Hypertension*, 9, 2007, 134-142.
20. Littlejohn TW, Majul CR, Olvera R, SeeberM, Results of Treatment With Telmisartan-Amlodipine in Hypertensive Patients, *Journal of Clinical Hypertension,* 11, 2009, 207-213.
21. Wald DS, Law M, Morris JK, Bestwick JP, Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 Trials, *American Journal of Medicine*, 122, 2009, 290-300.
22. Sica DA, Rationale for fixed-dose combinations in the treatment of hypertension: the cycle repeats, *Drugs* 62, 2002, 243–262.
23. Gradman AH, Acevedo C, Evolving strategies for the use of combination therapy in hypertension, *Current Hypertension Report*, 4, 2002, 343–9.
24. Chrysant SG, Antihypertensive effectiveness of low-dose lisinopril hydrochlorothiazide combination, *Archives of Internal Medicine,* 154, 1994, 737–743.
25. Brown CL, Backhouse CI, Grippat JC, Santoni JP, The effect of perindopril and hydrochlorothiazide alone and in combination on blood pressure and on the renin-

angiotensin system in hypertensive subjects, *European Journal of Clinical Pharmacology,* 1990, 39, 327-332.

26. Okpechi I, Rayner B, Schoeman H, Achieving blood preSsure goals study in uncontrolled hypeRtensive pAtients treated with a fixed-dose combination of ramipriL/hydrochlorothiazide: the ASTRAL study, *Cardiovascular Journal of Africa*, 22, 2011, 79-84.
27. Maeda K, Adachi M, Kinoshita A, Koh N, Efficacy and safety of the losartan-hydrochlorothiazide combination tablet in patients with hypertension uncontrolled by angiotensin II receptor antagonist therapy: the Aichi Research on Combination therapy for Hypertension (ARCH) study, *Internal Medicine,* 51, 2012, 1167-1175.
28. Carlberg B, Samuelsson O, Lindholm LH, Atenolol in hypertension: is it a wise choice? *Lancet,* 364, 2004, 1684–1689.
29. Lindholm LH, Carlberg B, Samuelsson O, Should b blockers remain first choice in the treatment of primary hypertension? A meta-analysis, *Lancet,* 366, 2005, 1545–1553.
30. Bradley HA, Wiysonge CS, Volmink JA, Mayosi BM, How strong is the evidence for use of beta-blockers as first-line therapy for hypertension? Systematic review and meta-analysis, *Journal of Hypertension*, 24, 2006, 2131–41.
31. Saunders E, Weir MR, Kong BW, Hollifield J, A comparison of the efficacy and safety of a beta blocker, a calcium channel blocker, and a converting enzyme inhibitor in hypertensive blacks, *Archives of Internal Medicine,* 150, 1990, 1707–1713.
32. Bateman DN, Dean CR, MucklowJC,Bulpitt CJ, Atenolol and chlorthalidone in combination for hypertension, *British Journal of Clinical Pharmacology*, 7, 1979, 357–63.
33. Stanton T, Reid JL, Fixed dose combination therapy in the treatment of hypertension, *Journal of Human Hypertension,* 16, 2002, 75-78.
34. Dahlof B, DeglInnocenti A, Elmfeldt D, Puig JG, Felodipine-metoprolol combination tablet: maintained health-related quality of life in the presence of substantial blood pressure reduction, American *Journal of Hypertension,* 18, 2005, 1313–1329.
35. Frishman WH, Hainer JW, Sugg J, A factorial study of combination hypertension treatment with metoprolol succinate extended release and felodipine extended release: results of the Metoprolol Succinate-Felodipine Antihypertension Combination Trial (M-FACT), *American Journal of Hypertension,* 19, 2006, 388–395.
36. 36.Mac Gregor GA, Markandu ND, Banks RA, Bayliss J, Roulston JE, Jones JC, Captopril in essential hypertension, contrasting effects of adding hydrochlorothiazide or propranolol, *British Medical Journal (Clinical research ed)*, 284, 1982, 693-696.
37. Sever Peter S, Messerli Franz H, Hypertension management 2011: optimal combination therapy, *European Heart Journal*, 32, 2011, 2499-2506.
38. Frishman WH, Ram CVS, McMahon FG, Graff A, Comparison of amlodipine and benazepril monotherapy to amlodipine plus benazepril in patients with systemic hypertension: a randomized, double-blind, placebo-controlled, parallel-group study, *Journal of Clinical Pharmacology,* 35, 1995, 1060–1066.
39. Philipp T, Smith TR, Glazer R,Wernsing M, Two multicenter, 8-week, randomized, double-blind, placebo controlled, parallel-group studies evaluating the efficacy and tolerability of amlodipine and valsartan in combination and as monotherapy in adult patients with mild to moderate essential hypertension, *Clinical Therapeutics,* 29, 2007, 563–580.
40. Chrysant SG, Melino M, Karki S, Lee J, The combination of olmesartanmedoxomil and amlodipine besylate in controlling high blood pressure: COACH, a randomized, double-blind, controlled, 8-week factorial efficacy and safety study, *Clinical Therapeutics*, 30, 2008, 587–604.
41. Gradman AH, Cutler NR, Davis PJ, Robbins JA, Combined enalapril and felodipine extended release (ER) for systemic hypertension, *American journal of cardiology,* 79, 1997, 431–435.
42. Jamerson K, Weber MA, Bakris GL, Dahlof B, For the accomplish Trial Investigators. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients, *New England Journal of Medicine,* 359, 2008, 2417–2428.
43. Egan CG, Pontremoli R, Role of the fixed-dose combination Lercanidipine-enalapril in renal protection.*Journal of Nephrology,* 24, 2011, 428-437.
44. Yusuf S, Teo KK, Pogue J, Young J, Telmisartan, ramipril, or both in patients at high risk for vascular events, *New England Journal of Medicine,* 358, 2008, 1547–1559.
45. Siscovick DS, Raghunathan TE, Psaty BM, Koepsell TD, Diuretic therapy for hypertension and the risk of primary cardiac arrest, *New England Journal of Medicine,* 330, 1994, 1852–1857.
46. Calhoun DA, Resistant or difficult-to-treat hypertension, *Journal of Clinical Hypertension,* 8, 2006, 181–186.
47. Davis TM, Millns H, Stratton IM, Holman RR, Risk factors for stroke in type 2 diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS)**,** *Archives of International Medicine journal,* 159, 1999, 1097-1103.
48. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, For the Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes**,** *New England Journal of Medicine,* 345, 2001, 851-860.
49. Fogari R, Derosa G, Zoppi A, Preti P, Effect of telmisartan amlodipine combination at different doses on urinary albumin excretion in hypertensive diabetic patients with microalbuminuria**,** *American Journal of Hypertension,* 20, 2007, 417-422.
50. Devabhaktuni M, Bangalore S, Fixed combination of amlodipine and atorvastatin in cardiovascular risk management: patient perspectives, *Vascular Health and Risk Management,* 5, 2009, 377-387.
51. Miura Y, Yamamoto N, Tsunekawa S, Taguchi S, Replacement of valsartan and candesartan by telmisartan in hypertensive patients with type 2 diabetes**,** *Diabetes Care,* 28,2005, 757-758.
52. Schupp M, Clemenz M, Gineste R, Witt H, Molecular characterization of new selective peroxisome proliferators

activated receptor γ modulators with angiotensin receptor blocking activity**,** *Diabetes,* 54, 2005, 3442-3452.

53. Hunt SA, ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelinesfor the Evaluation and Management of Heart Failure), *Journal of American College of Cardiology*, 47, 2006, 1503-1505.
54. Flack JM, Peters R, Mehra VC, Nasser SA, Hypertension in special populations, *Cardiology Clinics*, 20, 2002, 303-319.
55. Law MR, Wald NJ, Morris JK, Jordan RE, Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials, *British Medical Journal*, 326, 2003, 1427.
56. Zamboli P, De Nicola L, Minutolo R, Bertino V, Management of hypertension in chronic kidney disease, *Current Hypertension Report*, 8, 2006, 497-501.
57. Mogensen CE, Neldam S, Tikkanen I, Oren S, Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, micro albuminuria, and non-insulin dependent diabetes, the candesartan and lisinoprilmicro-albuminuria (CALM)study**,** *British Medical Journal,* 321, 2000, 1440-1444.
58. Nakao NN, Seno H, Kasuga H, Toriyama T, Effects of combination treatment with losartan and trandolapril on office and ambulatory blood pressures in non-diabetic renal disease, a COOPERATE-ABP sub study**,** *American Journal of Nephrology,* 24, 2004, 543-548.
59. Nakao N, Yoshimura A, Morita H, Takada M, Combination treatment of angiotensin-ii receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE) a randomised controlled trial**,** *Lancet,* 361, 2003, 117-124.
60. McKelvie RS, Rouleau JL, White M, Afzal R, Comparative impact of enalapril, candesartan or metoprololalone or in combination on ventricular remodelling in patients with congestive heart failure**,** *European Heart Journal,* 24, 2003, 1727-1734.
61. Ruggenenti P, Perna A, Loriga G, Ganeva M, Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial, *Lancet*, 365, 2005, 939-946.

Source of Support: Nil, **Conflict of Interest:** None.