Amlodipine/valsartan fixed-dose combination treatment in the management of hypertension: A double-blind, randomized trial

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Abstract

Background: To compare the fixed-dose combination (FDC) of amlodipine/valsartan 5/80mg with valsartan 160mg monotherapy for efficacy and safety in hypertensive patients.

Methods: We designed this double-blind, randomized, and noninferiority trial in which patients with elevated systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) were randomly assigned to receive amlodipine/valsartan 5/80mg FDC or valsartan 160mg monotherapy for 8 weeks. The primary endpoint was changes in office SBP and DBP from baseline to 8 weeks. Twenty-four-hour blood pressure (BP) and the incidence of adverse events were recorded.

Results: A total of 42 patients underwent randomization. At 8 weeks, office SBP changes were $-16.5 \pm 15.5$ mmHg ($p < 0.001$) with amlodipine/valsartan 5/80mg FDC and $-6.9 \pm 11.4$ mmHg ($p = 0.012$) with valsartan 160mg monotherapy while corresponding changes in office DBP were $-9.8 \pm 7.7$ mmHg ($p < 0.001$) and $-2.5 \pm 6.6$ mmHg ($p = 0.095$), respectively. The between-group differences were $-9.6$ mmHg (95% CI, $-18.1$ to $-1.1$; $p = 0.028$) for SBP and $-7.3$ mmHg (95% CI, $-11.8$ to $-2.8$; $p = 0.002$) for DBP. Furthermore, reductions in both 24-hour SBP ($-9.2$ mmHg; 95% CI, $-16.4$ to $-2.1$; $p = 0.013$) and DBP ($-4.6$ mmHg; 95% CI, $-9.2$ to $-0.1$; $p = 0.048$) were consistently greater with amlodipine/valsartan 5/80mg FDC than with valsartan 160mg. Overall, 27 and 23 adverse events occurred in the amlodipine/valsartan 5/80mg FDC group and in the valsartan 160mg monotherapy group, respectively. The majority were mild and were not related to study medications. There were no significant differences in safety between two treatments.

Conclusion: Efficacy of amlodipine/valsartan 5/80mg FDC was superior to that of valsartan 160mg monotherapy while both treatments were well-tolerated.

Keywords: Amlodipine; Fixed-dose combination; Hypertension; Valsartan

1. INTRODUCTION

Hypertension affects at least one-fifth of the world adult population. Evidence shows that lowering blood pressure (BP) reduces morbidity and mortality in patients at array of cardiovascular risk. In addition to nonpharmacologic interventions that improve BP, pharmacological agents provide the primary basis for hypertension management in the majority of patients. Among major antihypertensive agents, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), and thiazide (or thiazide-like) diuretics are preferentially recommended in the general condition because of their additional cardiovascular protection effects and/or accessibility.

Despite the availability of more effective antihypertensive agents, any antihypertensive monotherapy provides adequate BP control in a very limited number of patients. A majority of patients with hypertension, especially those at high risk, require two or more agents from different pharmacological classes to reach their BP goals. This underlines complexity in pathogenesis for hypertension. Therefore, an early combination of antihypertensive agents is a more appropriate treatment strategy than is initial high-dose monotherapy because of additive efficacy and theoretically fewer side effects. However, one of the caveats of the combination strategy in hypertension management is that adherence to treatment decreases when the number of pills prescribed to a patient increases.

The fixed-dose combination (FDC) pharmacologic products combining two or more active drugs in a single dosage form has
been widely accepted in treatment for infectious diseases. The FDC of two antihypertensive agents provides improvement in compliance when compared with the corresponding free-drug components given separately.\textsuperscript{10} Amlodipine, a long-acting dihydropyridine CCB, and valsartan, a nonpeptide ARB, are commonly prescribed first-line antihypertensive agents. Given that these two agents target pathophysiology that have potential counter-regulatory mechanisms,\textsuperscript{11} amlodipine/valsartan FDC might further enhance BP-lowering effects beyond improvement in compliance. The objective of this study was to compare efficacy and safety of amlodipine/valsartan 5/80 mg FDC with valsartan 160 mg monotherapy in patients with hypertension whose BP was not controlled with valsartan 80 mg monotherapy.

2. METHODS

2.1. Study design and oversight

This 8-week active-controlled, parallel-group, fixed-dose, double-blind, randomized, and noninferiority trial was conducted at Taipei Veterans General Hospital between June 2009 and September 2010. The trial was sponsored by Novartis and was conducted in accordance with the principles of the Declaration of Helsinki and the International Council on Harmonization Good Clinical Practice guidelines. The protocol and amendments were approved by the ethics committee. All patients provided written informed consent.

2.2. Study population

Patients who were 18 years of age and older and had mild to moderate essential hypertension that was uncontrolled on zero to one antihypertensive agent (defined as systolic BP [SBP] between 140 mmHg and 180 mmHg and/or diastolic BP [DBP] between 90 mmHg and 120 mmHg based on the office measurement) were enrolled. Patients at high cardiovascular risk (eg, those with diabetes mellitus, chronic kidney disease defined by the presence of microalbuminuria or an estimated glomerular filtration rate <60 mL/min per 1.73 m² of body surface area, established coronary heart disease or equivalents, or 10-y risk for cardiovascular disease ≥10% by the Framingham risk score) who had SBP between 130 mmHg and 180 mmHg and/or DBP between 80 mmHg and 120 mmHg were also eligible. All patients had received no or stable antihypertensive treatments for at least 4 weeks before screening. Key exclusion criteria included hypertension secondary to an identifiable and treatable cause; severe heart failure; a cerebrovascular event or myocardial infarction within the previous 3 months; clinically significant valvular heart diseases; and significant hepatic and/or renal dysfunction. In addition, patients who refused to stop agents known to affect BP were not eligible.

2.3. Study procedures

Figure 1 shows the study scheme. Eligible patients underwent a 4-week, single-blind, run-in period during which valsartan 80 mg monotherapy was given and other background antihypertensive agents were discontinued. Afterward, patients who met the inclusion criteria were then randomly assigned in a 1:1 ratio to receive amlodipine/valsartan 5/80 mg FDC or valsartan 160 mg monotherapy for 8 weeks. Permutated block (size of four) randomization was performed with the use of computer-generated random numbers provided by the sponsor. No stratification was applied. Amlodipine/valsartan 5/80 mg and valsartan 160 mg were provided as identical-appearing capsules in order to maintain blinding to the treatment.

At each visit, office BP was assessed using an oscillometric sphygmomanometer. All BP measurements were made on the same arm, in which higher BP was recorded during screening, at trough drug effect while patients were seated and rested for at least 5 minutes but not while they were left unattended. Two BP readings were taken and averaged readings were used for all analyses. Ambulatory blood pressure monitoring (ABPM) was completed at randomization and at the end of treatment or early withdrawal by the standard electronic ambulatory monitoring equipment worn by the patients for 24 hours.

2.4. Study endpoints

The primary endpoint was changes in office SBP and DBP from baseline to 8 weeks. The secondary endpoint was changes in 24-hour SBP and DBP from baseline to 8 weeks assessed by ABPM. Safety was assessed on the basis of vital signs, electrocardiography and laboratory evaluation, and adverse events (AEs) that occurred during the study and were coded with the use of the Medical Dictionary for Regulatory Activities.

2.5. Statistical analysis

The study was designed to test the hypothesis that the noninferiority of amlodipine/valsartan 5/80 mg FDC to valsartan 160 mg monotherapy with respect to the change in office SBP. Based on the prior experience on amlodipine/valsartan and valsartan,\textsuperscript{12} the change from baseline to the end of treatment in DBP between amlodipine/valsartan 5/80 mg FDC and valsartan 160 mg monotherapy was expected to be around 3 mmHg with a standard error of 1 mmHg. Therefore, the upper bound of 95% CI was set at 3 mmHg. Namely, if the upper bound of 95% CI for the between-group difference in the change in office SBP was less than the predefined noninferior margin of 3 mmHg, amlodipine/valsartan 5/80 mg FDC was considered to be noninferior to valsartan 160 mg monotherapy. Given a potential dropout, a sample size of 40 patients was estimated to provide adequate power at an alpha level of 0.05.

The primary efficacy analysis was conducted within the intention-to-treat (ITT) population that included all patients who underwent randomization and received at least one dose of study medications. The per-protocol (PP) population included all randomized patients who completed study medications without major protocol deviations. In addition, analyses for safety were performed based on the safety population that included all
randomized patients who had taken at least one dose of study medications. We reported compliance to study medications using data for tablets dispensed to, taken by, and returned from each patient.

Between-group differences were examined using the unpaired \( t \) test, the Mann-Whitney \( U \) test, the Pearson's chi-square test, or the Fisher's exact test as appropriate. Changes in BP from baseline within treatment groups were tested by the paired \( t \) test. All analyses were done with SAS version 8.2 (SAS Institute, Cary, NC, USA).

This trial is registered with ClinicalTrials.gov, number NCT01070043.

3. RESULTS

3.1. Patients

Between June 2009 and September 2010, 60 patients were screened and enrolled, among whom 42 (70.0%) underwent randomization (Fig. 2). The exposure of study treatments after randomization was not different between two groups (55.7 ± 2.9 d for the amlodipine/valsartan FDC group and 51.5 ± 15.4 d for the valsartan monotherapy group; \( p = 0.234 \)) and treatment compliance was >80% in all randomized patients. All of 42 patients were included in the ITT population and 38 patients were included in the PP population (two had permanent discontinuation of study medications because of AEs, another two had the protocol deviation due to failure to complete ABPM at the end of treatment, and all four were in the valsartan monotherapy group).

The baseline characteristics of patients are shown in Table 1. The mean age of patients was 57.3 years and 40.5% were women. Among patients who underwent randomization, 15 patients (35.7%) had coronary heart disease and 27 patients (64.3%) had comorbid condition equivalent to coronary heart disease. Overall, 20 patients (47.6%) had estimated 10-year risk for cardiovascular disease ≥10%. Demographic and clinical characteristics were well balanced between two groups at baseline. Although office SBP was higher in the amlodipine/valsartan FDC group than in the valsartan monotherapy group (150.3 ± 12.9 mmHg vs 141.1 ± 12.7 mmHg; \( p = 0.026 \)), there was no difference in baseline ambulatory BP between two groups.

3.2. Efficacy

In the ITT population, there were significant changes from baseline to 8 weeks in office BP in both groups except for office DBP in the valsartan monotherapy group (Fig. 3A). The between-group difference in the change in office SBP was –9.6 mmHg (95% CI, -18.1 to -1.1). Since the upper limit of 95% CI was less than the predefined noninferior margin (3 mmHg) and did not include zero, amlodipine/valsartan 5/80 mg FDC was considered to be superior to valsartan 160 mg monotherapy with regard to the reduction in office SBP (\( p = 0.028 \)). In parallel with 8-week changes in office SBP, changes in office DBP were significantly greater in the amlodipine/valsartan FDC group than in the valsartan monotherapy group with a between-group difference of –7.3 mmHg (95% CI, -11.8 to -2.8; \( p = 0.002 \) for superiority). Consistent with the finding in the ITT population, upper limits of 95% CI of effect estimates for between-group differences in 8-week changes in office BP were also within the predefined noninferior margin (between-group difference, –9.3 mmHg [95% CI, -18.9 to 0.1] for the change in office SBP; –6.9 mmHg [95% CI, -11.8 to -1.9] for the change in office DBP) in the PP population (Fig. 3B). In the exploratory analysis, the proportion of patients having notable reductions in either SBP (>20 mmHg) or DBP (>10 mmHg) or in both was greater in the amlodipine/valsartan FDC group than in the valsartan monotherapy group (Table 2).

With regard to the secondary efficacy endpoint, Figure 4 presents 8-week changes in mean 24-hour BP from baseline in the ITT population. At 8 weeks, changes in mean 24-hour SBP were –14.7 ± 11.6 mmHg in the amlodipine/valsartan FDC group and –5.5 ± 11.4 mmHg in the valsartan monotherapy group, whereas changes in mean 24-hour DBP were –7.7 ± 7.4 mmHg in the amlodipine/valsartan FDC group and –3.0 ± 7.2 mmHg in the valsartan monotherapy group.

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Fig. 2 Flow diagram. ABPM = ambulatory blood pressure monitoring; AE = adverse event; FDC = fixed-dose combination; ITT = intention to treat.
3.3. Safety
Throughout the study, the proportion of patients reporting AEs was similar for both treatment groups (Table 3). Most AEs (92.0%) were mild in intensity and were not related to study medications when being judged by investigators. One serious AE occurred before randomization and there was none during the double-blind phase.

There were no significant changes from baseline in either treatment group or between treatment groups for physical findings and laboratory analyses, including electrocardiography.

### Table 1
Baseline characteristics of patients

|                     | Amlodipine/valsartan FDC (n=21) | Valsartan monotherapy (n=21) | p     |
|---------------------|---------------------------------|-----------------------------|-------|
| Age, y              | 59.5 ± 13.8                     | 55.1 ± 11.8                 | 0.280 |
| Female sex, n (%)   | 9 (42.9)                        | 8 (38.1)                    | 0.753 |
| Weight, kg          | 70.1 ± 13.6                     | 73.6 ± 11.3                 | 0.367 |
| Smoking, n (%)      | 7 (33.3)                        | 7 (33.3)                    | >0.999|
| Medical history     |                                 |                             |       |
| CHD, n (%)          | 9 (42.9)                        | 6 (28.6)                    | 0.334 |
| CHD risk equivalent, n (%)<sup>a</sup> | 13 (61.9) | 14 (66.7)  | 0.747 |
| Chronic kidney disease, n (%)<sup>b</sup> | 5 (23.8)  | 2 (9.5)    | 0.410 |
| Diabetes, n (%)     | 3 (14.3)                        | 4 (19.0)                    | >0.999|
| Framingham 10-y cardiovascular disease risk of 10% or greater, n (%)<sup>c</sup> | 9 (42.9) | 11 (52.4) | 0.901 |
| Pulse rate, beats per minute | 81.8 ± 12.0 | 80.7 ± 10.2 | 0.742 |
| Office BP, mmHg     |                                 |                             |       |
| SBP                 | 150.3 ± 12.9                    | 141.1 ± 12.7                | 0.026 |
| DBP                 | 92.1 ± 10.8                     | 90.0 ± 9.4                  | 0.218 |
| Ambulatory BP, mmHg |                                 |                             |       |
| 24-h SBP            | 144.4 ± 17.4                    | 139.8 ± 13.5                | 0.342 |
| 24-h DBP            | 87.0 ± 14.1                     | 87.9 ± 9.4                  | 0.799 |

BP = blood pressure; CHD = coronary heart disease; DBP = diastolic blood pressure; FDC = fixed-dose combination; SBP = systolic blood pressure.

<sup>a</sup>CHD risk equivalents include abdominal aortic aneurysm, carotid artery disease, and peripheral arterial disease.

<sup>b</sup>Nine patients were excluded because of no valid data.

### Table 2
Blood pressure response rate

|                     | Amlodipine/valsartan FDC (n=21) | Valsartan monotherapy (n=20) | p     |
|---------------------|---------------------------------|-----------------------------|-------|
| SBP reduction >20 mmHg, n (%) | 10 (47.6) | 2 (10.0) | 0.008 |
| DBP reduction >10 mmHg, n (%)  | 11 (52.4) | 4 (20.0) | 0.031 |
| SBP reduction >20 mmHg and/or DBP reduction >10 mmHg, n (%)  | 14 (66.7) | 4 (20.0) | 0.003 |

DBP = diastolic blood pressure; FDC = fixed-dose combination; SBP = systolic blood pressure.

One patient in the valsartan group did not have the blood pressure assessment at 8 wks.

### 4. DISCUSSION
In this double-blind, randomized, and noninferiority trial, we found that, in patients with mild to moderate hypertension, after 8-week treatment, amlodipine/valsartan 5/80 mg FDC provided better BP management than did valsartan 160 mg monotherapy (greater reductions in office SBP, office DBP, and ambulatory SBP). AEs that led to study medication discontinuation were rare as both treatments were well-tolerated.

Despite widely recognized importance of BP control, BP goal attainment rates are disturbing. Treatment compliance is an essential factor for BP goal attainment. Efficacy and safety of the treatment are determinants of how patients are adherent to. Although efficacy on reductions in BP, major cardiovascular events, and mortality is similar among the first-line antihypertensive agents,8,14,15 side effects vary. ARBs, compared with ACE inhibitors, are better tolerated with lower rates of cough and angioedema.16–19 Adherence is better with ARBs, which even have a treatment discontinuation rate similar to placebo,20 and with CCBs. In addition to synergic efficacy on BP reductions, combing an ARB with a CCB reduces the risk of CCB-associated peripheral edema.21,22 Treatment complexity compromises its adherence. The FDC of antihypertensive agents in a single tablet provides improvement in compliance when compared with the corresponding free-drug components given separately. It simplifies treatment, and therefore, improves BP control. In addition, end organ damage is the function of BP and duration. The previous observation suggests that a more rapid BP reduction is preferred to delayed treatment.23 In this 8-week study, about two-third of patients in the amlodipine/valsartan FDC group had either reduction...
in SBP/DBP greater than 20/10 mmHg, whereas only a quarter of patients in the valsartan monotherapy group reached such reductions. Although the goal of BP control is a moving target, it is indisputable that the right combination treatment provides a greater opportunity for a prompt reduction in BP before irreversible end organ damage accrues.5,26

In addition to office SBP, 24-hour SBP measured by ABPM independently predicts cardiovascular morbidity and mortality.27 Our study showed that patients in both amlodipine/valsartan FDC and valsartan monotherapy groups had significant response on both SBP and DBP reductions assessed by ABPM and patients in the amlodipine/valsartan FDC group experienced a greater reduction in ambulatory SBP than those in the valsartan monotherapy group.

Our study has several limitations. Firstly, the sample size by the study design and an a priori statistic hypothesis only required 20 patients for each treatment group. Although the small sample size may produce spurious results as CIs reported in our primary endpoint were wide, BP changes assessed by the office measurement were consistent with those assessed by ABPM. Furthermore, the extent to which office BP was reduced by FDC and by monotherapy was compatible to prior experience on the “Rule of 10/5”.28 Secondly, baseline office SBP was higher in the amlodipine/valsartan FDC group than in the valsartan monotherapy group. Therefore, the regression to the mean phenomenon might be more apparent in the amlodipine/valsartan FDC group. For every 10 mmHg above 154 mmHg in baseline SBP, a further decrease of 1 mmHg in SBP with treatment is expected. In a properly-sized randomized trial, any discrepancies in baseline characteristics should be considered chance. As the between-group difference in changes in office BP was greater than 1 mmHg, we believe our findings will be still valid in another trial that level off this nominal difference. Moreover, there was a parallelly greater reduction in DBP with amlodipine/valsartan FDC than with valsartan monotherapy when no between-group difference in baseline DBP existed.

In conclusion, efficacy, evidenced by office BP reductions, of amlodipine/valsartan 5/80 mg FDC is superior to that of valsartan 160 mg monotherapy while both treatments were well-tolerated.

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**REFERENCES**

1. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet* 2017;389:37–55.
2. Sundström J, Arima H, Jackson R, Turnbull F, Rahimi K, Chalmers J, et al; Blood Pressure Lowering Treatment Trials’ Collaboration. Effects of blood pressure reduction in mild hypertension: a systematic review and meta-analysis. Ann Intern Med 2015;162:184–91.

3. Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocoo MV, et al; SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 2015;373:2103–16.

4. Cushman WC, Ford CE, Cutler JA, Margolis KL, Davis BR, Grimm RH, et al; ALLHAT Collaborative Research Group. Success and predictors of blood pressure control in diverse North American settings: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). J Clin Hypertens (Greenwich) 2002;4:393–404.

5. Dahlöf B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, et al; ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amloidipine 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 randomised controlled trial. Lancet 2005;366:895–906.

6. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes. UKPDS 38. BMJ 1998;317:703–13.

7. 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.

8. Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. Am J Med 2009;122:290–300.

9. Gupta P, Patel P, Strauch B, Lai FY, Akbarov A, Gulsin GS, et al. Biochemical screening for nonadherence is associated with blood pressure reduction and improvement in adherence. Hypertension 2017;70:1042–8.

10. Gupta AK, Arshad S, Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: a meta-analysis. Hypertension 2010;55:399–407.

11. Cappuccio FP, Markandu ND, Sagnella GA, Singer DR, Buckley MG, Miller MA, et al. Effects of amloidipine on urinary sodium excretion, renin-angiotensin-aldosterone system, atrial natriuretic peptide and blood pressure in essential hypertension. J Hum Hypertens 1991;5:115–9.

12. Philipp T, Smith TR, Glazer R, Wernsing M, Yen J, Jin J, et al. Two multicenter, 8-week, randomized, double-blind, placebo-controlled, parallel-group studies evaluating the efficacy and tolerability of amloidipine and valsartan in combination and as monotherapy in adult patients with mild to moderate essential hypertension. Clin Ther 2007;29:563–80.

13. Mills KT, Bandy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, et al. Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries. Circulation 2016;134:441–50.

14. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet 2016;387:957–67.

15. Turnbull F; Blood Pressure Lowering Treatment Trials’ Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet 2003;362:1527–35.

16. Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, et al; ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008;358:1547–59.

17. Pitt B, Poole-Wilson PA, Segal R, Martinez FA, Dickstein K, Camm AJ, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II. Lancet 2000;355:1582–7.

18. Pfeffer MA, McMurray JJV, Velazquez EJ, Rouleau JL, Kober L, Maggioni AP, et al; Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med 2003;349:1893–906.

19. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993–1004.

20. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment in hypertension: 9. Discontinuations for adverse events attributed to different classes of antihypertensive drugs: meta-analyses of randomized trials. J Hypertens 2016;34:1921–32.

21. Makani H, Bangalore S, Romero J, Weyer-Pinzon O, Messerli FH. Effect of renin-angiotensin system blockade on calcium channel blocker-associated peripheral edema. Am J Med 2011;124:128–35.

22. Fogari R, Zoppa A, Derosa G, Mugellini A, Lazzari P, Rinaldi A, et al. Effect of valsartan addition to amloidipine on ankle oedema and subcutaneous tissue pressure in hypertensive patients. J Hum Hypertens 2007;21:220–4.

23. Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, 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;363:2022–31.

24. Chiang CE, Wang TD, Lin TH, Yeh HI, Liu PY, Cheng HM, et al. The 2017 focused update of the guidelines of the Taiwan Society of Cardiology (TSOC) and the Taiwan Hypertension Society (THS) for the management of hypertension. Acta Cardiol Sin 2017;33:213–25.

25. Williams B, Mancia G, Spiering W; Agabiti Rosei E, Azizi M, Burnier M, et al; ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension: the 2018 ESH/ESC Guidelines for the management of arterial hypertension. Eur Heart J 2018;39:3021–104.

26. Gupta A, Mackay J, Whitehouse A, Godec T, Collier T, Pocock S, et al. Long-term mortality after blood pressure-lowering and lipid-lowering treatment in patients with hypertension in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) Legacy study: 16-year follow-up results of a randomised factorial trial. Lancet 2018;392:1227–37.

27. Huang CM, Wang KL, Cheng HM, Chuang SY, Sung SH, Yu WC, et al. Central versus ambulatory blood pressure in the prediction of all-cause and cardiovascular mortalities. J Hypertens 2011;29:454–9.

28. Chiang CE, Wang TD, Ueng KC, Lin TH, Yeh HI, Chen CY, et al. 2015 guidelines of the Taiwan Society of Cardiology and the Taiwan Hypertension Society for the management of hypertension. J Clin Med Assoc 2015;78:1–47.