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REVIEW

Clinical utility of fixed-combination telmisartan–amlodipine in the treatment of hypertension

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Abstract: The majority of hypertensive patients, especially those with target organ damage, are likely to require multiple-drug therapy in order to reach blood pressure (BP) targets and reduce their risk of adverse vascular outcomes. The rationale for combination therapy with agents that block the renin–angiotensin system (RAS) and a calcium channel blocker (CCB) or diuretic is well founded in growing evidence. Recent published trials have shown that the combination of an RAS suppressor and a dihydropiridinic CCB would offer additional benefits independently of BP reduction. A telmisartan–amlodipine combination has demonstrated significantly greater BP reductions compared with each monotherapy component in the overall population, and in particular in patients with moderate to severe hypertension and high-risk patients. This combination is well tolerated with a safety profile similar to placebo and is consistent with the known safety profile of its monotherapy components.

Keywords: hypertensive patients, monotherapy, stroke, antihypertensive

Introduction

Cardiovascular disease (CVD) places a significant burden on healthcare providers. Despite improvements in morbidity and mortality statistics in some countries over the past few decades, atherosclerotic CVD remains the leading cause of morbid events and mortality worldwide, with the expectation of an increasing prevalence in developing countries.[1,2] Worldwide, ischemic heart disease and cerebrovascular disease are projected to account for 24% of total deaths by 2030.[1] In the EU alone, where CVD causes 1.5 million deaths each year,[3] direct healthcare costs currently amount to €105 billion, with 57% of the total due to inpatient care.[4] CVD is also associated with substantial indirect costs due to lost productivity, with an estimated overall annual cost to the EU of around €169 billion.[4]

High blood pressure (BP) is the single most prevalent risk factor for CVD worldwide. It is responsible for more deaths than any other risk factor.[5,6] A meta-analysis has shown that for each increase in systolic BP (SBP) of 20 mm Hg and in diastolic BP (DBP) of 10 mm Hg, there is at least a doubling in the risk of mortality from ischemic heart disease and stroke.[7] Attributed to 54% of cerebrovascular disease and 47% of ischemic heart disease worldwide in 2001, high BP was responsible for 7.6 million premature deaths or 13.5% of the global total.[5] However, only half of this burden was in patients with clinical hypertension, indicating that lesser degrees of BP elevation remain a cause for concern.[5]

Patients with elevated BP alone are not considered to be at high risk of a CV event such as myocardial infarction (MI) or stroke. However, the presence of hypertension adds to

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a patient's CV risk profile when other risk factors are present.[8] "CV high-risk patients" include those patients with atherothrombotic disease, as indicated by a history of MI, stroke, transient ischemic attack, or peripheral arterial disease, together with patients with multiple risk factors and patients with target organ damage associated with type 2 diabetes.[9–13] CV high-risk patients are in the middle of the spectrum of risk for CVD progression that is referred to as the "CV continuum".[14,15]

Although lifestyle intervention can improve a patient's CV risk profile and has a fundamental role in the management of all CV high-risk patients,[16] pharmacological agents that are able to modify the disease processes involved in CVD and delay its progression may become instrumental in reducing the burden of CVD. In this regard, statins, antiplatelet therapy, hypoglycemic agents in type 2 diabetes, and antihypertensive therapy have all shown a benefit in reducing CV risk.[17–20] A continuous and linear relationship has been shown between BP lowering and reduction in CV mortality, with the risk reduction approximately constant for any given BP level down to an SBP of 115 mm Hg and a DBP of 75 mm Hg for all age groups.[7,20] Even a small reduction in SBP of 2 mm Hg would predictably lower mortality from ischemic heart disease and stroke by 7% and 10%, respectively.[7] A recent study in patients with type 2 diabetes has indicated that aggressive BP lowering of SBP to $<$120 mm Hg, however, may not confer additional benefit compared with usual control.[21] Similar results have been published in African American hypertensive patients.[22] A recent reappraisal of the European guidelines for management of hypertension reinforces the scarce evidence to support tighter BP control in order to reduce the risk of CV events in hypertensive patients.[23]

Thus, based on BP-lowering effects alone, the treatment of CV high-risk patients with antihypertensive therapy represents an opportunity to modify CV risk and improve patient outcomes. In order to overcome the challenges of achieving BP control in these patients,[24,25] the ideal antihypertensive medication should be safe and well tolerated, provide efficacious and long-lasting 24-hour BP reductions as monotherapy with additional efficacy when used in combination, and reduce or slow the pathological processes that lead to target organ damage and CV events.[26,27] In this regard, blockade of the renin–angiotensin system (RAS) is a potent therapeutic approach, offering the potential to reduce organ damage not only by reducing BP but also by reducing the inflammatory disease that leads to atherosclerosis.[28]

The majority of hypertensive patients, especially those with target organ damage, are likely to require multiple-drug therapy in order to reach BP targets and reduce their risk of adverse vascular outcomes.[29,30] The rationale for combination therapy with agents that block RAS and a calcium channel blocker (CCB) or diuretic is well founded.[30–33] Recent landmark studies, such as ACCOMPLISH (Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension) and ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm), have demonstrated the antihypertensive benefits associated with angiotensin-converting enzyme (ACE) inhibitor/CCB combinations.[34–36] More recently, the combination of an angiotensin receptor blocker (ARB), such as valsartan or olmesartan, and amlodipine has been introduced and tested in stage 1 and 2 hypertensive patients as well as on those not controlled by monotherapy.[37,38]

This review will focus on the role of the combination telmisartan–amlodipine, a potent ARB and the most frequently used CCB, to achieve adequate BP targets in hypertensive patients.

Pharmacology, rationale for combination, and pharmacokinetics of fixed-combination telmisartan–amlodipine

Telmisartan is an orally active nonpeptide that lowers BP with once-daily dosing by blocking the type I angiotensin II receptor (AT1 receptor), thus selectively inhibiting the pressor effects of the RAS. Telmisartan was approved by the US Food and Drug Administration (FDA) in November 1998 and by the European Commission in December 1998 for the treatment of hypertension. More recently, in ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial), telmisartan demonstrated a noninferior capacity than ramipril to prevent CV events in high-risk patients.[39] As a consequence of these results, the FDA has approved an expanded indication for telmisartan that can now be used to reduce the risk of MI, stroke, or death from CV causes in patients aged 55 years or older who are intolerant to ACE inhibitors but at high risk for CV events.

Amlodipine is a dihydropyridine CCB that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle cells. It is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in BP. Amlodipine was approved by the FDA in July 1992. The first European approval was in July 1989.

The pharmacokinetics of repeated oral doses of 80 mg telmisartan at steady state alone and in combination with

repeated oral doses of amlodipine 10 mg at steady state were studied in a two-way crossover, open, randomized design study (trial 1235.2). This study included 38 healthy male or female Caucasian volunteers aged 18–50 years. A second pharmacokinetic (drug interaction) study (study 502.126) was also conducted in 12 healthy subjects as part of the Micardis® monotherapy development program. This open-label, randomized, two-sequence, two-period crossover study demonstrated that telmisartan 120 mg had no effect on the steady-state pharmacokinetics of amlodipine 10 mg. In summary, there is no clinically significant change in systemic exposure to telmisartan 80 mg on coadministration of amlodipine 10 mg after dosing both medications to steady state, and there is no relevant drug–drug interaction with regard to the effect of amlodipine on telmisartan.

Efficacy studies and comparative trials

The telmisartan–amlodipine clinical development program included a pivotal 8-week, double-blind, randomized, placebo-controlled trial with a factorial study design (including a large ambulatory blood pressure monitoring [ABPM] substudy) to demonstrate the additive nature of combining telmisartan and amlodipine across a wide range of doses of each of the individual components.[40] An analysis of the prospectively defined subset of patients with moderate to severe hypertension at baseline has also been published.[41] The results of the 24-hour ABPM substudy have also been published.[42]

A total of 2607 patients were enrolled in the factorial study between April 2006 and November 2006, and 1461 patients were randomized and treated for up to 8 weeks. A total of 1344 (92%) patients completed the 8-week trial. The efficacy analyses were performed on all patients with a baseline value and at least one efficacy measurement at target dose (n = 1423). Both telmisartan (irrespective of amlodipine dosage; $P < 0.0001$) and amlodipine (irrespective of telmisartan dosage; $P < 0.0001$) significantly lowered the in-clinic trough diastolic BP, without evidence of counterproductive telmisartan-by-amlodipine interaction at any dosage (not involving patients treated with placebo; $P = 0.1777$). As expected, the greatest least-squares mean reductions in in-clinic diastolic and systolic BP were observed with combination therapy compared with respective monotherapies (Figure 1). The greatest overall reduction in BP was observed with the telmisartan 80 mg plus amlodipine 10 mg combination (mean reduction in systolic BP/diastolic BP: −26.4 mm Hg/−20.1 mm Hg; $P < 0.05$ vs both monotherapies).[40] More than 50% of all patients treated with combination therapy achieved BP control (diastolic BP < 90 mm Hg and systolic BP < 140 mm Hg), with the highest percentages (76.5% [overall control] and 85.3% [diastolic BP control]) being achieved by patients treated with telmisartan 80 mg plus amlodipine 10 mg. Diastolic BP response and systolic BP response was achieved by 91.2% and 90.4% of patients in the telmisartan 80 mg plus amlodipine 10 mg group, respectively.[40] This combination was also effective in patients with moderate or severe hypertension. In fact, the greatest reduction in BP (SBP/DBP −26.5 ± 1.2/−21 ± 0.8 mm Hg) was achieved with the highest-dose combination of telmisartan 80 mg plus amlodipine 10 mg and the SBP/DBP response rates >90%. The BP control (<140/90 mm Hg) and DBP control (<90 mm Hg) obtained with this combination was 77% and 85%, respectively.[41]

The largest reductions in 24-hour mean BP were observed with the combination of telmisartan 80 mg and amlodipine 10 mg when compared with their respective monotherapies ($P < 0.0001$ in each comparison): telmisartan 80 mg and amlodipine 10 mg (–22.4/–14.6 mm Hg), telmisartan 80 mg (–11.0/–6.9 mm Hg), and amlodipine 10 mg (–11.9/–6.9 mm Hg). Greater BP reductions were also observed for the combinations of lower doses of telmisartan (40 mg) and amlodipine (5 mg) in combination compared with the components.[42]

Fogari et al[43] evaluated the effect of a combination therapy with telmisartan and amlodipine on urinary albumin excretion rate (UAER) in hypertensive patients with type 2 diabetes and microalbuminuria and examined whether two different dose regimens (high-dose telmisartan/low-dose amlodipine and vice versa) offered different benefits in terms of reduction of proteinuria. After a 2-week placebo washout period, during which antihypertensive but not oral antidiabetic drugs were discontinued, patients fulfilling the inclusion criteria were treated with the telmisartan (40 mg)/amlodipine (2.5 mg) combination. After 4 weeks, patients whose BP was not controlled (BP > 130/80 mm Hg) were enrolled in the study and randomized to two different dose titration regimens: one based on increasing doses of telmisartan (40 mg every 4 weeks until 160 mg) and a fixed 2.5 mg dose of amlodipine (group T), the other based on an increasing dose of amlodipine (2.5 mg every 4 weeks until 10 mg) and a fixed 40 mg dose of telmisartan (group A). After 16 weeks, the nonresponder patients were given 0.1 mg/day transdermic clonidine.[43] High-dose telmisartan/low-dose amlodipine and low-dose telmisartan/high-dose amlodipine combinations produced similar reductions in systolic and diastolic BP values, with no significant differences between the

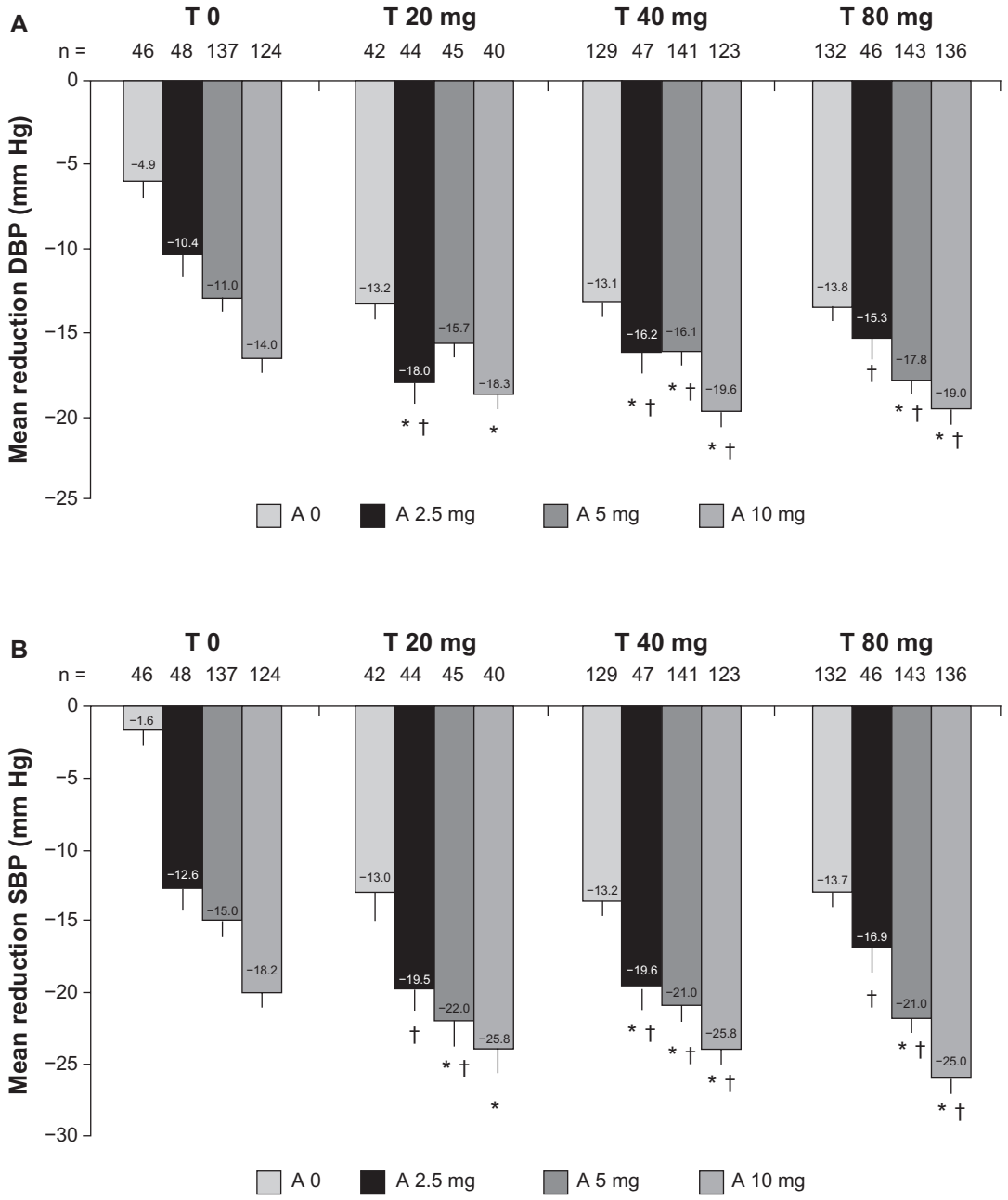

Figure 1 Effect of 8 weeks of treatment with telmisartan (T) 0 mg, 20 mg, 40 mg, and 80 mg plus amlodipine (A) 0 mg, 2.5 mg, 5 mg, and 10 mg on the change from baseline in the in-clinic seated trough (**A**) diastolic blood pressure (DBP) (mm Hg) or (**B**) systolic blood pressure (SBP) (mm Hg).
Notes: *$P < 0.05$ vs T monotherapy; †$P < 0.05$ vs A monotherapy. Data are least-squares mean (standard error) values adjusted for dosage, country/region, and baseline blood pressure.

two regimens at any time of the study. With increasing doses of telmisartan (from 40 mg to 80 mg, 120 mg, and 160 mg), systolic/diastolic BP values were reduced from baseline by 16/10 mm Hg ($P < 0.01$ vs baseline), 24/21 mm Hg, 23/21 mm Hg, and 24/21 mm Hg (all $P < 0.001$ vs baseline), respectively. With increasing doses of amlodipine (from 2.5 mg to 5 mg, 7.5 mg, and 10 mg), systolic/diastolic BP values were reduced from baseline by 16/10 mm Hg ($P < 0.01$ vs baseline), 25/22 mm Hg, 25/21 mm Hg, and 25/22 mm Hg (all $P < 0.001$ vs baseline), respectively. The UAER was significantly decreased from baseline by both combination regimens, but such a decrease was significantly more marked in the T group (Figure 2). Reductions of UAER from baseline were of 34.6 mg/24 hours ($P < 0.05$ vs baseline), 62.9 mg/24 hours ($P < 0.01$ vs baseline and $P < 0.05$ vs A group), 86.5 mg/24 hours ($P < 0.001$ vs baseline and $P < 0.01$ vs A group) and 102 mg/24 hours ($P < 0.0001$ vs baseline and $P < 0.001$ vs A group) for telmisartan 40 mg,

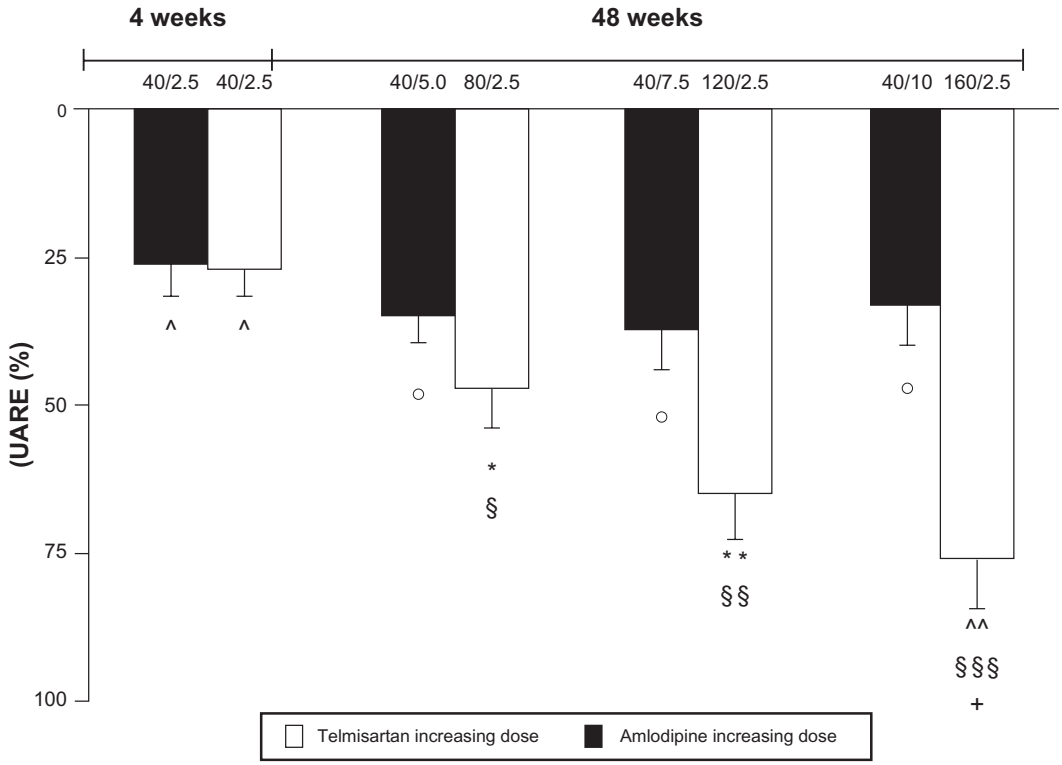

Figure 2 Percentage of urinary albumin excretion rate (UAER) decrease with telmisartan–amlodipine combination at different doses.
Notes: ^*p* <0.05, ^^*p* <0.0001, °*p* <0.03 °*p* <0.01, °°*p* <0.001, Change from baseline; §*p* <0.05; §§*p* <0.01, §§§*p* <0.001, between treatment, +*p* <0.05 vs 80/2.5.

80 mg, 120 mg, and 160 mg/amlodipine 2.5 mg daily, respectively. Reductions of UAER from baseline were of 35.1 mg/24 hours ($P < 0.05$ vs baseline), 46.2 mg/24 hours ($P < 0.03$ vs baseline), 50.3 mg/24 hours ($P < 0.03$ vs baseline), and 45 mg/24 hours ($P < 0.03$ vs baseline) for amlodipine 2.5 mg, 5 mg, 7.5 mg, and 10 mg/telmisartan 40 mg daily, respectively.[43]

Safety and tolerability

In the factorial study, a total of 545 (37.3%) patients reported at least one adverse event during the 8-week study.[40] When analyzed by treatment groupings, the percentage of patients reporting adverse events on specific treatment was comparable: placebo (39.1%, n = 18), telmisartan monotherapy (36.8%, n = 113), amlodipine monotherapy (36.1%, n = 115), and combination therapy (37.9%, n = 299) groups. The most commonly reported adverse events were headache (5.4%, n = 79) and peripheral edema (4.4%, n = 65). Headache was more frequent in the placebo group (10.9%, n = 5) compared with the telmisartan monotherapy (5.9%, n = 18), amlodipine monotherapy (6.0%, n = 19), and combination therapy (4.7%, n = 37) groups. The incidence of peripheral edema was highest in the amlodipine 10 mg group (17.8%, n = 23); however, this rate was lower when amlodipine was used in combination with telmisartan: 11.4% (telmisartan 20 mg/amlodipine 10 mg), 6.2% (telmisartan 40 mg/amlodipine 10 mg), and 11.3% (telmisartan 80 mg/amlodipine 10 mg) (Figure 3).

Patient-focused perspectives such as quality of life, patient satisfaction/acceptability, adherence, and uptake

Hypertension is a chronic disease for which there is no cure. Antihypertensive medications will lower BP in patients for as long as patients comply with therapy. Poor patient adherence with health-related advice, medication, tests, and clinic appointments has been reported as the most common cause of nonresponse to medication.[44] Poor adherence to medication regimens is a major contributor to the gap between practice guidelines and clinical outcome in CVD.[45–47] Poor persistence may be affected by many patient-related factors. Poor motivation to accept treatment can lead to a cycle of treatment failure. Patients and physicians frequently accept failure of initial treatment and lack the motivation to continue treating the condition. Patients may embark on a series of treatment steps, each viewed as a failure, further undermining motivation and fulfilling negative expectations, resulting in poor BP control and an increased risk of mortality and morbidity for the patient. In consequence, poor compliance and persistence

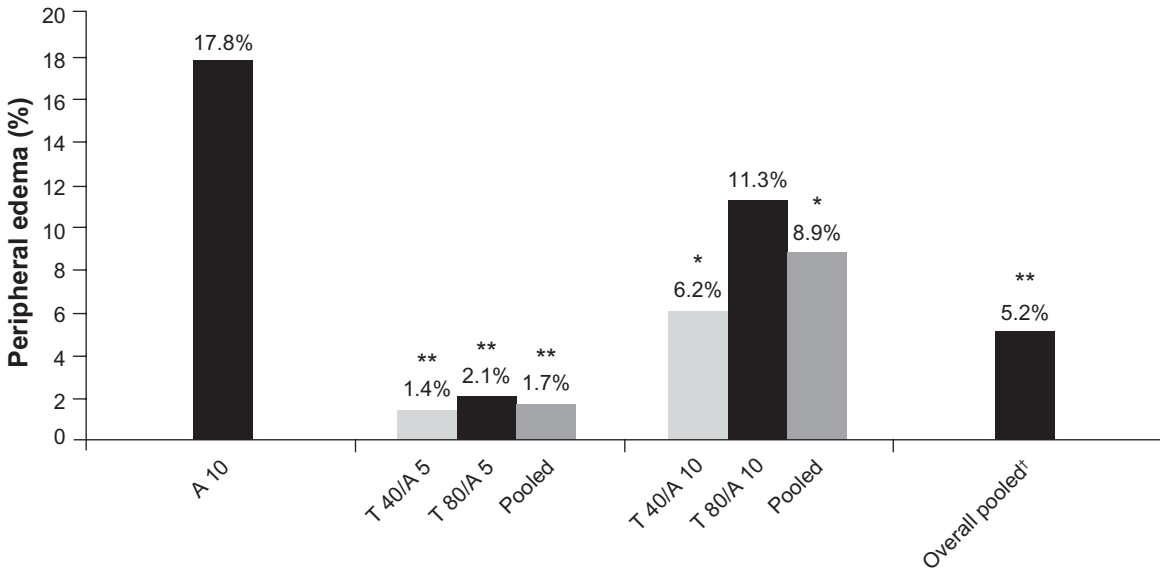

Figure 3 Incidence of peripheral edema (%) in the amlodipine 10 mg (A10) group compared with combinations (telmisartan 40 mg [T40] or 80 mg [T80] plus amlodipine 5 mg [A5] or 10 mg).
Notes: *$P < 0.05$; **$P < 0.0001$ vs A10.

with medication by patients results in poor clinical outcomes. Given the scale of the problem and its effect on everyday practice, it is essential to develop and implement strategies to improve compliance.

Persistence rates with currently available classes of antihypertensive medications vary widely. Patients prescribed ARBs as their initial medication are more likely to persist with treatment than patients on other classes of antihypertensive.[48] Moreover, it has been confirmed that the treatment discontinuation rate differs between antihypertensive drug classes. The treatment discontinuation rate is lowest in patients in whom the drug initially prescribed was an ARB, and became progressively greater with the initial administration of an ACE inhibitor, a CCB, an α-blocker, a β-blocker, and a diuretic.[49]

The use of multiple medications and complexity of treatment regimen are two of the major determinants of poor medication adherence. A survey conducted by the National Council on Patient Information and Education showed that one-third of patients receive at least two prescriptions and 10% of patients receive four or more prescriptions after a visit to a primary care physician.[50] In a systematic review of the impact of dose regimen on medication compliance, it has been shown that dose taking was inversely related to the prescribed number of doses per day. Compliance was significantly higher for once daily versus three times daily ($P = 0.008$), once daily versus four times daily ($P < 0.001$), and twice daily versus four times daily ($P = 0.001$) regimens.[51] Adherence to antihypertensive agents varies inversely with dosing frequency,[52] and nonadherent patients tend to have higher BP than adherents.[53] As adherence rates are inversely related to the number of drugs given, it would be expected that patients would be more adherent when they take a combination of drugs as a single tablet than if they are given the same drugs as two separate pills, even when dosed once daily.[54,55] In the 2009 reappraisal of European guidelines on hypertension management, the European Society of Hypertension Task Force notes: "Whenever possible, use of single pill (or single pill) combinations should be preferred, because simplification of treatment carries advantages for compliance to treatment".[23]

Conclusion

Adequate BP control and reduction of CV events are particularly effective with the combination of antihypertensive agents, including an ACE inhibitor or an ARB. Recently, the combination of an ACE inhibitor or ARB plus a CCB appears to be rational and effective. These combinations can thus be recommended for priority use. Telmisartan–amlodipine combination has demonstrated significantly larger DBP and SBP reductions compared with each monotherapy component in the overall population, and in particular in patients with moderate to severe hypertension. This combination is well tolerated with a safety profile similar to placebo and is consistent with the known safety profile of its monotherapy components.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Mathers CD, Loncar D. Projects of global mortality and burden of disease from 2002 to 2030. *PLoS Med*. 2006;3(11):e442.
2. Ezzati M. Estimates of global and regional potential health gains from reducing multiple major risk factors. *Lancet*. 2003;362(9380): 271–280.
3. Petersen S, Peto V, Rayner M, et al. *European Cardiovascular Disease Statistics*. London, UK: British Heart Foundation; 2005.
4. Leal J, Luengo-Fernández R, Gray A, et al. Economic burden of cardiovascular diseases in the enlarged European Union. *Eur Heart J*. 2006; 27(13):1610–1619.
5. Lawes CM, Vander Hoom S, Rodgers A. International Society of Hypertension. Global burden of blood pressure-related disease, 2001. *Lancet*. 2008;371(9623):1513–1518.
6. Lopez AD, Mathers CD, Ezzati M, et al. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet*. 2006;367(9524):1747–1757.
7. Lewington S, Clarke R, Qizilbash N, et al. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360(9349): 1903–1913.
8. 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(6):1105–1187.
9. Steg PG, Bhatt DL, Wilson PW, et al. One-year cardiovascular event rates in outpatients with atherothrombosis. *JAMA*. 2007;297(11): 1197–1206.
10. Capewell S, Murphy NF, MacIntyre K, et al. Short-term and long-term outcomes in 133,429 emergency patients admitted with angina or myocardial infarction in Scotland,1990–2000: population-based cohort study. *Heart*. 2006;92(11):1563–1570.
11. Dhamoon MS, Sciacca RR, Rundek T, et al. Recurrent stroke and cardiac risks after first ischemic stroke: the Northern Manhattan Study. *Neurology*. 2006;66(5):641–646.
12. Cea-Calvo L, Conthe P, Gómez-Fernández-Pérez C. RICARHD Investigators. Target organ damage and cardiovascular complications in patients with hypertension and type 2 diabetes in Spain: a cross-sectional study. *Cardiovasc Diabetol*. 2006;5:23.
13. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364(9438): 937–952.
14. Dzau V, Braunwald E. Resolved and unresolved issues in the prevention and treatment of coronary artery disease: a workshop consensus statement. *Am Heart J*. 1991;121(4 Pt 1):1244–1263.
15. Dzau VJ, Antman EM, Black HR, et al. The cardiovascular disease continuum validated: clinical evidence of improved patient outcomes: part I: Pathophysiology and clinical trial evidence (risk factors through stable coronary artery disease). *Circulation*. 2006;114(25): 2850–2870.
16. Bakris G, Böhm M, Dagenais G, et al. Cardiovascular protection for all individuals at high risk: evidence-based best practice. *Clin Res Cardiol*. 2008;97(10)713–725.
17. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomized trials of statins. *Lancet*. 2005;366(9493):1267–1278.
18. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high-risk patients. *BMJ*. 2002; 324(7329):71–88.
19. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med*. 2009; 360(2):129–139.
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(5):385–407.
21. The ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med*. 2010;362(17):1575–1585.
22. Appel LJ, Wright JT Jr, Greene T, et al. AASK Collaborative Research Group. Intensive blood-pressure control in hypertensive chronic kidney disease. *N Engl J Med*. 2010;363(10):918–929.
23. 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(11):2121–2158.
24. Wolf-Maier K, Cooper RS, Kramer H, et al. Hypertension treatment and control in five European countries, Canada, and the United States. *Hypertension*. 2004;43(1):10–17.
25. Wong ND, Lopez VA, L'Italien G, et al. Inadequate control of hypertension in US adults with cardiovascular disease comorbidities in 2003–2004. *Arch Intern Med*. 2007;167(22):2431–2436.
26. Mustone Alexander L. Desirable therapeutic characteristics of an optimal antihypertensive agent. *Drugs*. 2006;66(9):1239–1252.
27. Mulcahy D. Circadian variation in cardiovascular events. *Blood Press Monit*. 1998;3(1):29–34.
28. Schmieder RE, Hilgers KF, Schlaich MP, Schmidt BM. Renin-angiotensin system and cardiovascular risk. *Lancet*. 2007;369(9568):1208–1219.
29. Wang YR, Alexander GC, Stafford RS. Outpatient hypertension treatment, treatment intensification, and control in Western Europe and the United States. *Arch Intern Med*. 2007;167(2):141–147.
30. Tedesco MA, Natale F, Calabro R. Effects of monotherapy and combination therapy on blood pressure control and target organ damage: a randomized prospective intervention study in a large population of hypertensive patients. *J Clin Hypertens*. 2006;8(9):634–641.
31. Weir MR. Targeting mechanisms of hypertensive vascular disease with dual calcium channel and renin-angiotensin system blockade. *J Hum Hypertens*. 2007;21(10):770–779.
32. Egan BM. Combination therapy with an angiotensin converting enzyme inhibitor and a calcium channel blocker. *J Clin Hypertens*. 2007;9(10): 783–789.
33. Epstein M, Bakris G. Newer approaches to antihypertensive therapy. Use of fixed-dose combination therapy. *Arch Intern Med*. 1996;156(17): 1969–1978.
34. Weber MA, Bakris GL, Dahlof B, et al. Baseline characteristics in the Avoiding Cardiovascular Events Through Combination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial: a hypertensive population at high cardiovascular risk. *Blood Press*. 2007;16(1):13–19.
35. Dahlof B, Sever PS, Poulter NR, et al. 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 randomised controlled trial. *Lancet*. 2005;366(9489):895–906.
36. Kjeldsen SE, Jamerson KA, Bakris GL, et al. Predictors of blood pressure response to intensified and fixed combination treatment of hypertension: the ACCOMPLISH study. *Blood Press*. 2008;17(1):7–17.
37. Allemann Y, Fraile B, Lambert M, et al. Efficacy of the combination of amlodipine and valsartan in patients with hypertension uncontrolled with previous monotherapy: the Exforge in Failure After Single Therapy (EX-FAST) study. *J Clin Hypertens*. 2008;10(3): 185–194.
38. Chrysant SG, Melino M, Karki S, et al. The combination of olmesartan medoxomil and amlodipine besylate in controlling high blood pressure: COACH, a randomized, double-blind, placebo-controlled, 8-week factorial efficacy and safety study. *Clin Ther*. 2008;30(4): 587–604.
39. ONTARGET Investigators, Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358(15):1547–1559.

40. Littlejohn TW 3rd, Majul CR, Olvera R, et al. Results of treatment with telmisartan-amlodipine in hypertensive patients. *J Clin Hypertens (Greenwich)*. 2009;11(4):207–213.
41. Littlejohn TW 3rd, Majul CR, Olvera R, et al. Telmisartan plus amlodipine in patients with moderate or severe hypertension: results from a subgroup analysis of a randomized, placebo-controlled, parallel-group, 4 × 4 factorial study. *Postgrad Med*. 2009;121(2):5–14.
42. White WB, Littlejohn TW, Majul CR, et al. Effects of telmisartan and amlodipine in combination on ambulatory blood pressure in stages 1–2 hypertension. *Blood Press Monitor*. 2010;15(4):205–212.
43. Fogari R, Derosa G, Zoppi A, et al. Effect of telmisartan-amlodipine combination at different doses on urinary albumin excretion in hypertensive diabetic patients with microalbuminuria. *Am J Hypertens*. 2007;20(4):417–422.
44. Murphy J, Coster G. Issues in patient compliance. *Drugs*. 1997;54(6):797–800.
45. Michalsen A, Konig G, Thimme W. Preventable causative factors leading to hospital admission with decompensated heart failure. *Heart*. 1998;80(5):437–441.
46. Gehi AK, Ali S, Na B, et al. Self-reported medication adherence and CV events in patients with stable coronary heart disease: the heart and soul study. *Arch Inter Med*. 2007;167(16):1798–1803.
47. Sokol MC, McGuigan KA, Verbrugge RR, et al. Impact of medication adherence on hospitalization risk and healthcare cost. *Med Care*. 2005;43(6):517–520.
48. Esposti LD, Di Martino M, Saragoni S, et al. Pharmacoeconomics of antihypertensive drug treatment: an analysis of how long patients remain on various antihypertensive therapies. *J Clin Hypertens*. 2004;6(2):76–84.
49. Corrao G, Zambon A, Parodi A, et al. Discontinuation of and changes in drug therapy for hypertension among newly-treated patients: a population-based study in Italy. *J Hypertens*. 2008;26(4):819–824.
50. Dezii CM. Medication noncompliance: what is the problem? *Manag Care*. 2000;9(9 Suppl):7–12.
51. Claxton AJ, Cramer JA, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther*. 2001;23(8):1296–1310.
52. Sica D. Single pill combination antihypertensive drugs. Do they have a role in rational therapy? *Drugs*. 1994;48(1):16–24.
53. Bramley TJ, Gerbino PP, Nightengale BS, Frech-Tamas F. Relationship of blood pressure control to adherence with antihypertensive monotherapy in 13 managed care organizations. *J Manag Care Pharm*. 2006;12(3):239–245.
54. Bangalore S, Kamalakkannan G, Parkar S, et al. Fixed-dose combinations improve medication compliance: a meta-analysis. *Am J Med*. 2007;120(8):713–719.
55. Gupta AK, Arshad S, Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: a meta-analysis. *Hypertension*. 2010;55(2):399–407.