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REVIEW

Choice of ACE inhibitor combinations in hypertensive patients with type 2 diabetes: update after recent clinical trials

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Abstract: The diabetes epidemic continues to grow unabated, with a staggering toll in micro- and macrovascular complications, disability, and death. Diabetes causes a two- to four-fold increase in the risk of cardiovascular disease, and represents the first cause of dialysis treatment both in the UK and the US. Concomitant hypertension doubles total mortality and stroke risk, triples the risk of coronary heart disease and significantly hastens the progression of microvascular complications, including diabetic nephropathy. Therefore, blood pressure reduction is of particular importance in preventing cardiovascular and renal outcomes. Successful antihypertensive treatment will often require a combination therapy, either with separate drugs or with fixed-dose combinations. Angiotensin converting enzyme (ACE) inhibitor plus diuretic combination therapy improves blood pressure control, counterbalances renin-angiotensin system activation due to diuretic therapy and reduces the risk of electrolyte alterations, obtaining at the same time synergistic antiproteinuric effects. ACE inhibitor plus calcium channel blocker provides a significant additive effect on blood pressure reduction, may have favorable metabolic effects and synergistically reduce proteinuria and the rate of decline in glomerular filtration rate, as evidenced by the GUARD trial. Finally, the recently published ACCOMPLISH trial showed that an ACE inhibitor/calcium channel blocker combination may be particularly useful in reducing cardiovascular outcomes in high-risk patients. The present review will focus on different ACE inhibitor combinations in the treatment of patients with type 2 diabetes mellitus and hypertension, in the light of recent clinical trials, including GUARD and ACCOMPLISH.

Keywords: type 2 diabetes, blood pressure, ACE inhibitor

Introduction

The diabetes epidemic continues to grow.[1] In the year 2000, there were an estimated 171 million patients worldwide with a diagnosed diabetes, and this number is projected to rise to 366 million in 2030,[2] 90% of whom will have a type 2 diabetes. At the time of diagnosis, about 50% of type 2 diabetics are also hypertensives. This percentage increases even more in the presence of micro- or macroalbuminuria.[3] Microalbuminuria (urinary albumin excretion of 20 to 200 μg/min or 30 to 299 mg/24 hours), which often heralds the onset of diabetic nephropathy, independently predicts cardiovascular morbidity and mortality in diabetic patients.[4–6]

Blood pressure (BP) reduction is a major priority in preventing clinical events in patients with type 2 diabetes mellitus and hypertension, who are at very high risk of cardiovascular and renal outcomes. Diabetes causes a two- to fourfold increase in the risk of cardiovascular disease,[7,8] including stroke,[9] atrial fibrillation, flutter, coronary heart disease (CHD) and left ventricular hypertrophy,[10] and it is the first cause of renal

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replacement therapy both in the UK[11] and the US,[12] where over 40% of dialyzed patients are diabetics. Concomitant hypertension doubles total mortality and stroke risk, triples the already high risk of CHD and significantly hastens the progression of diabetic nephropathy,[13] retinopathy[14] and neuropathy.[15] In such patients, a difference of 5 mmHg in either systolic blood pressure (SBP) or diastolic blood pressure (DBP) increases the risk of cardiovascular events or death by 20% to 30%.[16] As a consequence, the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure,[17] the European Society of Hypertension[6] and the American Diabetes Association[18] all recommend achieving a target of <130/80 mmHg in subjects with diabetes and hypertension.

Successful treatment of these patients will often require a combination therapy,[19] either with separate drugs or with fixed-dose combinations.

Both of these offer several advantages: first, they allow a tighter BP control, and consequently a greater reduction of clinical endpoints, minimizing at the same time the risk of adverse effects, by using relatively small doses of two drugs in combination or by selecting agents that counteract each other's side effects.[20] As showed by an extensive analysis of 354 randomized trials of the five main categories of BP lowering drugs,[21] antihypertensive efficacy of drugs in combination was additive, but prevalence of adverse effects was less than additive. In 66 trial arms, single drugs caused symptoms in 5.2% of participants (3.6%–6.6%), while in 33 trial arms two drugs together caused symptoms in 7.5% (5.8%–9.3%), which is significantly lower than the value of 10.4% (twice 5.2%) expected with an additive effect ($p = 0.03$).

Secondly, in many cases less time is required to achieve target BP, with equivalent[22] or better[23] tolerability than higher dose monotherapy. Finally, patients with comorbidities, such as type 2 diabetes and hypertension, may benefit from the effects of different antihypertensive combinations, that may offer specific cardio-, vasculo- and renoprotective advantages that go beyond BP reduction per se.

Fixed-dose combination therapy simplifies the treatment regimen, improving compliance and preventing treatment failures caused by missed doses.[24] Moreover, it usually allows cost reductions to the health care system.[23] On the other hand, it is not always possible to achieve the same medications and dosages in a combined pill, fixed-dose combinations do not allow easy dose adjustment,[25] exposing patients to the risk of orthostatic hypotension (ie, older patients, diabetic autonomic neuropathy), and tablet size is sometimes excessive.[26]

Combination therapy with separate drugs makes it easy to obtain the desired dose, and adjust it when needed. However, potential disadvantages include patient's perception that taking more medications is equated with being sicker,[25] and generally increased costs.

In hypertensive type 2 diabetics, commonly used combination therapies include an angiotensin converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) plus a diuretic or a calcium channel blocker (CCB). In the present review, we will focus on two combinations:

1. ACE inhibitor plus diuretic
2. ACE inhibitor plus CCB

ACE inhibitor plus diuretic

Rationale of the combination

ACE inhibitors were able to decrease cardiovascular morbidity and mortality in the diabetic cohort of a number of trials, including the Heart Outcomes Prevention Evaluation Trial,[27] the Captopril Prevention Project Trial (CAPPP),[28] the Fosinopril versus Amlodipine Cardiovascular Events randomized Trial (FACET),[29] the Appropriate BP Control Diabetes (ABCD) Trial[30] and the UK Prospective Diabetes Study,[19] even if a meta-analysis of the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) demonstrated the primary importance of BP lowering for reducing cardiovascular risk in patients with or without diabetes mellitus, independently of drug classes.[31] In any case, renin-angiotensin system (RAS) blockade may delay deterioration in glomerular filtration rate (GFR) and progression of albuminuria,[32,33] and the renoprotective effects of RAS blockade have been shown in a number of landmark trials in patients with type 2 diabetes mellitus;[34–36] comparative data from the Diabetics Exposed to Telmisartan And EnalaprIL Trial (DETAIL) established that the ACE inhibitor enalapril and the ARB telmisartan conferred similar renoprotection in patients with hypertension and early type 2 diabetic nephropathy.[37] However, RAS blockade may inhibit urinary potassium excretion, and hyperkalemia remains a clinician's major concern particularly in patients with or at risk for chronic kidney disease.[38]

Diuretics (usually thiazides or thiazide-like indoline diuretics such as indapamide) remain among the most effective treatments for elevated BP.[17] In the aforementioned BPLTTC analysis,[31] diuretics appear to reduce cardiovascular events to a degree similar to ACE inhibitors, beta-blockers or CCBs. Moreover, in 13 101 adults with hypertension and type 2 diabetes, enrolled in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a thiazide-type diuretic, chlorthalidone,

decreased cardiovascular complications to an extent similar to an ACE inhibitor, lisinopril, or a CCB, amlodipine.[39] At low doses, thiazide diuretics usually do not cause changes in renal function,[40] and they can be used when the estimated GFR is > 30 mL/min. However, diuretics may cause urinary electrolyte wasting, and consequently hyponatremia, hypokalemia and/or hypomagnesemia. In addition, diuretic-induced volume reduction may activate the renin-angiotensin system, limiting their hypotensive action,[41,42] and cause pre-renal azotemia. Finally, thiazide diuretics may cause metabolic adverse effects, including hyperuricemia, hypercholesterolemia and glucose intolerance, increasing a patient's likelikood of developing diabetes and worsening glycemic control in diabetic patients.[43,44] About 50% of the hyperglycemic effects of thiazides is thought to be the result of decreased insulin release from the pancreatic β-cell, mediated by the reduction in serum potassium below 3.5 mEq/L.[45] In fact, total body potassium stores play a central role in the control of insulin secretion,[46] probably because ATP-sensitive K^+ channels couple β-cell metabolism to electrical activity. A recent analysis of the Systolic Hypertension in Elderly Program (SHEP)[47] showed that incidence of new diabetes is related to the severity of hypokalemia, even after adjusting for baseline glucose and the dose of diuretic. The absolute increase in the incidence of diabetes mellitus was much less when serum potassium concentration dropped from 5.0 to 4.5 mEq/L but much higher when serum potassium dropped from 4.0 to 3.5 mEq/L. In any case, it has to be noted that even when there were no changes in kalemia the incidence of diabetes was about double with placebo than with thiazide, and that K^+ supplementation in SHEP did not prevent new-onset diabetes. In the recently published Mechanisms for the Diabetes Preventing Effect of Candesartan (MEDICA) trial,[48] a multicenter 3-way crossover trial, 26 non-diabetic, obese hypertensives underwent 12-week treatment periods with candesartan, hydrochlorothiazide (HCTZ) and placebo; after 12 weeks on thiazides (compared to candesartan), visceral and hepatic fat accumulation, higher inflammation markers (C-reactive protein, serum amyloid), glycated hemoglobin and transaminases were observed; in addition, insulin sensitivity was reduced after HCTZ versus candesartan or placebo, independently of changes in kalemia. As a consequence, the diabetogenic effects of thiazides are most likely multifactorial, with a clear non-K^+ dependent component.[49]

Therefore, the combination of an ACE inhibitor with a diuretic has a strong physiopathological rationale (Table 1); it allows improved BP control,[50–53] it counterbalances RAS activation secondary to diuretic therapy and reduces the risk of hyper- or hypokalemia, obtaining at the same time synergistic antiproteinuric effects.[54] Additionally, high sodium intake generally blunts the antiproteinuric effects of RAS blockers; the use of thiazide diuretics overcomes this blunting effect.[55–57] Moreover, the combination of an ACE inhibitor with a diuretic is particularly useful in African-American patients, where monotherapy with conventional doses of RAS blocking agents is often unsuccessful or marginally successful.[58] Finally, ACE inhibitors may at least theoretically mitigate the alterations in glucose metabolism induced by diuretics.[59] Numerous clinical investigations have shown that ACE inhibitors can improve insulin action on whole-body and skeletal muscle glucose disposal in insulin-resistant and hypertensive subjects, through multiple mechanisms. For example, the acute administration of captopril during a euglycemic glucose clamp caused a 25% increase in whole-body insulin sensitivity.[60] After the acute administration of captopril in type 2 diabetic subjects, a decreased daily glucose profile and increased postprandial forearm blood flow were also observed.[61] Even acute oral administration of the ACE inhibitor captopril at lower doses, which has no effect on BP, was able to improve peripheral insulin-stimulated glucose disappearance in insulin-resistant individuals.[62] As discussed in an extensive review,[63] chronic administration of ACE inhibitors is usually associated with increased insulin sensitivity.[64,65] Large intervention trials have provided evidence that ACE inhibitor monotherapy may have a positive impact on glucose metabolism. In the Heart Outcomes and Prevention Evaluation (HOPE) study,[66] 3.6% of the patients in the ramipril group developed diabetes, compared with 5.4% in the placebo group ($p < 0.001$). In the FACET,[29] both fosinopril and amlodipine decreased fasting serum glucose and serum insulin in patients with type 2 diabetes mellitus and hypertension. In the ALLHAT trial,[67] only 8.1% of the patients randomized to lisinopril developed diabetes, compared with 11.6% in the diuretic group. A network meta-analysis[68] showed that

Table 1 Advantages of ACE inhibitor/diuretic combination therapy

Improved blood pressure control
Counterbalances renin-angiotensin system activation secondary to diuretic therapy
Reduced risk of electrolyte disorders (eg, hyper- or hypokalemia, hypomagnesemia)
Synergistic antiproteinuric effects, particularly in the presence of high sodium intake
Better therapeutic response in African-American patients
Blunts the adverse metabolic effects induced by the diuretic

hyperglycemia and subsequent diabetes occur more often in patients receiving diuretics (or beta-blockers) instead of ACE inhibitors (or ARBs). However, only a limited number of studies has explored the metabolic effects of ACE inhibitor/diuretic combination therapy. In 1983, two multicenter trials compared the effects of an ACE inhibitor, captopril, combined with a diuretic to the administration of either agent alone in mild to moderate hypertensives.[69] In addition to BP, effects on serum potassium, uric acid, glucose, and cholesterol were examined. The first study (study A) was conducted on 210 hypertensives randomly assigned to receive HCTZ 15 mg 3 times daily, captopril 25 mg 3 times daily or captopril plus HCTZ for 6 weeks. The second study (study B) involved 415 patients randomly assigned to receive captopril 25 mg twice daily plus HCTZ 25 mg twice daily, captopril 50 mg twice daily plus HCTZ 25 mg twice daily, captopril 50 mg twice daily plus placebo, HCTZ 25 mg twice daily plus placebo, or placebo alone for 6 weeks. In both studies, all patients except those receiving placebo only had significant BP reductions ($p < 0.05$). In both studies, those treated with HCTZ alone had a significant ($p < 0.05$) reduction in serum potassium and increases in uric acid, glucose and cholesterol when compared to captopril alone, where no significant changes in these parameters were observed in the combination arms. In another study,[58] 255 essential hypertensive patients were assigned to receive HCTZ, captopril, or both. With HCTZ alone, significant decreases in serum potassium, increases in uric acid, blood glucose, and blood cholesterol were observed ($p < 0.05$). With captopril alone, no changes in any of these parameters were seen. When captopril was added to HCTZ, attenuation of the diuretic effect on potassium and uric acid was significant, and the significant changes in blood sugar and cholesterol seen with the diuretic alone were prevented. In a small trial,[70] 10 hypertensive patients with type 2 diabetes mellitus were treated for 8 weeks with enalapril 20 mg/day and then divided in 2 groups of 5 patients each for an additional 8 weeks of treatment with enalapril alone or in combination with HCTZ; no significant difference was observed in any of the metabolic characteristics, including insulin sensitivity, between the values after 8 weeks of enalapril alone and the final values of the enalapril-treated and the enalapril/HCTZ-treated groups. In a 12-week multi-center dose-response study in 353 patients with essential hypertension,[71] combination therapy with zofenopril/HCTZ (30/12.5 mg/day or 60/12.5 mg/day) was more effective in maintaining continuous 24-hour BP control than either agent administered alone; the occurrence of treatment-related adverse events was comparable among the treatment groups, and the most common adverse events were cough and polyuria. Treatment withdrawal occurred in only 1.7% of patients. There were no increases in low-density lipoprotein cholesterol levels or triglycerides, blood glucose or uric acid levels with combination therapy. However, concerns about the metabolic effects of ACE inhibitor/diuretic combination therapy in hypertensive type 2 diabetics have been raised by other trials,[72,73] even if a recent large randomized trial, ADVANCE, did not show any deterioration in glycemic control in type 2 diabetics randomized to an ACE inhibitor, perindopril, plus a thiazide-like diuretic, indapamide.[74] In any case, while the metabolic effects of ACE inhibitor plus diuretic combinations are still a matter of debate, available evidence strongly supports the metabolic benefits of the ACE inhibitor/CCB combination, particularly in patients with prediabetes (glucose intolerance, metabolic syndrome or history of gestational diabetes) or diabetes mellitus (see below).

Although ACE inhibitors and diuretics have been individually used in a large number of trials on cardiovascular or renal endpoints, head-to-head comparisons between ACE inhibitor/diuretic combinations and other drugs or placebo in hypertensive type 2 diabetics are still a rarity.

Cardiovascular endpoints

In the Preterax in Albuminuria Regression (PREMIER) trial,[75] which enrolled 457 microalbuminuric, hypertensive, type 2 diabetics (see below), analysis of serious cardiovascular adverse events showed an incidence of 2.5% (6 of 244) in the perindopril/indapamide group versus 6.3% (15 of 237) in the enalapril group (relative risk [RR] 2.65, 95% confidence interval [CI] 1.03–6.83, $p = 0.036$). Combination therapy allowed a greater SBP (−14.8 mmHg) and DBP (−8.8) reduction, as compared to enalapril monotherapy (SBP −12.3 mmHg, DBP −7.3 mmHg).

In the Perindopril Protection Against Recurrent Stroke Study,[76] a total of 6105 patients with a history of stroke or transient ischemic attack were randomized to either perindopril with the discretional addition of the diuretic indapamide or placebo. 58% of participants received a combination therapy, in order to maximize the decrease in BP. The aim of the trial was to determine the effects of active treatment on major CV events among patients with a history of cerebrovascular disease. Of 6105 randomized participants, 761 had diabetes at baseline (88% type 2 diabetes),[77] with a mean SBP of 149 mmHg and a mean DBP of 84 mmHg. During the 4 years of follow-up, diabetic patients had a 35% (95% CI 10–64, $p = 0.004$) additional risk of stroke.

The RR estimates for total major vascular events among diabetic participants were 0.54 (95% CI 0.35–0.82) and 1.35 (95% CI 0.87–2.1) (p homogeneity = 0.003) for patients assigned at baseline to receive combination (perindopril plus indapamide) and single-drug therapy, respectively. Likely, the greater BP reduction produced by combination therapy may explain part of the protection against macrovascular events.

The Action in Diabetes and Vascular Disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) study[74] was designed to assess the effects on vascular disease of a fixed combination of the ACE inhibitor perindopril and the diuretic indapamide. In this study, 11,140 patients with type 2 diabetes, at least one additional risk factor and a wide range of BP values (mean baseline SBP: 145 mmHg; mean baseline DBP: 81 mmHg) were randomized to double-blind treatment with either perindopril-indapamide (n = 5 569) or placebo (n = 5 571). Primary study outcome was a composite of major macrovascular (cardiovascular [CV] death, non-fatal myocardial infarction [MI], non-fatal stroke) and microvascular (new or worsening nephropathy and retinopathy) events. After a mean of 4.3 years of follow-up, active therapy reduced SBP by 5.6 mmHg and DBP by 2.2 mmHg, as compared to placebo. 861 patients (15.5%) in the perindopril/indapamide group and 938 (16.8%) in the placebo group reached the primary outcome (relative risk reduction: 9%; 95% CI 0%–17%; p = 0.041). The effects of active treatment on major macro- or microvascular outcomes were similar (8% vs 9%), though not separately significant. The RR of death from CV disease was reduced by 18% (p = 0.03) and death from any cause by 14% (p = 0.03). There was no evidence of an interaction between the effect of treatment and baseline SBP, considered as a continuous variable.

Renal endpoints

In an old trial comparing the long-term effects of ACE inhibitors and CCBs in the treatment of type 2 diabetes associated with hypertension,[78] 102 patients normo- (n = 44), micro- (n = 36) or macroalbuminuric (n = 22) were randomly allocated to either nifedipine (n = 52) or enalapril (n = 50). Indapamide 2.5 mg/day or furosemide (up to 120 mg/day) were added if the BP remained high. At 1 year, 76% of the patients in the enalapril arm required the addition of diuretic treatment, as compared with only 14% in the nifedipine arm. Treatment with enalapril (and diuretic) reduced proteinuria significantly more than nifedipine, in all patients and also in the micro- and macroalbuminuric groups separately, despite a significantly higher BP in the enalapril than in the nifedipine arm of the trial ($p < 0.001$).

The Preterax in Albuminuria Regression (PREMIER) trial[75] was designed as a 12-month, randomized, controlled, double-blind, two-parallel group study. 457 patients with type 2 diabetes, hypertension and microalbuminuria were randomized to either low-dose combination of perindopril and indapamide (n = 233) or enalapril monotherapy (n = 224). Primary endpoint was the reduction of albumin excretion rate (AER). The perindopril/indapamide combination resulted in a statistically significant reduction in both BP (ΔSBP −3.05 mmHg, 95% CI −5.6/−0.4, p = 0.012; ΔDBP −1.5 mmHg, 95% CI: −3/−0.1, p = 0.019) and AER (−42%, 95% CI −50 to −33%; versus −27%, 95% CI −37/−16% with enalapril). Additionally, the greater AER reduction remained significant after adjustment for mean BP. Tolerability was comparable between therapies, with 47 adverse events in the combination versus 48 in the enalapril arm; the most frequent ones were cough (perindopril/indapamide 3.7%, enapril 2.1%) and dizziness (perindopril/indapamide 1.2%, enalapril 2.1%).

In the aforementioned ADVANCE trial, the following renal events were taken into account: development of micro- or macroalbuminuria, doubling of serum creatinine level to a level of at least 200 μmol/L, need for renal replacement therapy, or death from renal disease. During the follow-up period there were 1243 (22.3%) total renal events in the perindopril-indapamide group versus 1500 (26.9%) in the placebo group, with a relative risk reduction of 21% (95 CI 15%–7%, $p < 0.0001$). A nearly significant reduction in new or worsening nephropathy was also observed (RR reduction: 18%; 95% CI −1 to −32%; p = 0.055). Of particular importance in the setting of primary prevention of diabetic nephropathy (ie, normoalbuminuric patients), there was a significant reduction in the onset of microalbuminuria (RR reduction: 21%; 95% CI 14%–27%; $p < 0.0001$). Thus, over 5 years, 1 patient in every 20 assigned active treatment would have avoided 1 renal event, mainly the development of microalbuminuria. However, the most important factors that prevent the progression of renal damage in diabetes mellitus are the improvement of blood glucose control and a tighter BP control. In the ADVANCE trial, a reduction of 5.6 mmHg in SBP was observed among patients randomized to receive perindopril and indapamide, as compared with those assigned to receive placebo. Additionally, the same 11,140 patients were also randomized to undergo either a strategy of intensive blood glucose control (target glycated hemoglobin ≤6.5%) or a strategy of standard glucose control,[79] and intensive control reduced the incidence of combined major- or microvascular

events by 10% (hazard ratio [HR] 0.9, 95% CI 0.82–0.98, p = 0.01) and the incidence of nephropathy by 21% (HR 0.79, 95% CI 0.66–0.93, p = 0.006). As a consequence, the specific role of the fixed-dose combination of perindopril and indapamide in reducing the risk of new or worsening nephropathy is difficult to establish.

ACE inhibitor plus CCB

Rationale of the combination

The effects of RAS blockade in patients with type 2 diabetes and hypertension have already been described. Contrasting results have been reported on the CV effects of CCBs in diabetic hypertensive patients. In the Swedish Trial in Old Patients with hypertension-2 (STOP-2),[80] 719 diabetic and hypertensive patients aged 70 to 84 years were assigned to calcium antagonists (felodipine or isradipine, N = 231), ACE inhibitors (enalapril or lisinopril, N = 235) or conventional treatment (diuretics or beta-blockers, N = 253). The BP-lowering effects were similar in the three treatment groups. Treatment effects did not differ significantly for frequency of the primary endpoint (CV mortality). On the contrary, the ABCD trial, comparing enalapril and nisoldipine in 470 patient with non-insulin dependent diabetes and hypertension, was stopped prematurely because of a significantly higher incidence of MI among those randomized to CCB.[30] In the Irbesartan versus amlodipine Diabetic Nephropathy Trial,[35] 1715 hypertensive patients with type 2 diabetic nephropathy were randomized to either irbesartan or amlodipine or placebo. After 2.6 years of follow-up, the treatment with CCB, compared with ARB, provided the same incidence of major CV events, CV death, and total mortality. Finally, the FACET trial,[29] which enrolled 380 hypertensive type 2 diabetics randomly assigned to open-label fosinopril or amlodipine and followed up for 3.5 years, found a higher incidence of the combined outcome of acute MI, stroke, or hospitalized angina among patients assigned to amlodipine. However, those trials (STOP-2, ABCD, IDNT and FACET) are head-to-head comparisons between CCBs and agents blocking the RAS, and a few of them may suffer from a number of methodological flaws.[81] In fact, CCBs compared with conventional therapy are able to reduce the risk of non-fatal stroke by 25%,[82] thanks to their antiatherogenic[83–85] and antithrombotic[86,87] properties. On the other hand, CCBs (mainly dihydropyridinic) could increase the risk of MI,[82] through an increased adrenergic stimulation. Finally, dihydropyrinidic CCBs may commonly cause ankle edema, through three different mechanisms: arteriolar vasodilation, impairment of the local vascular autoregulation of blood flow and impaired protection against hydrostatic load.[88] Differences in sympathetic overactivation after arterial vasodilatation may lead to different ankle edema rates. So, dihydropyridinic CCBs that activate the sympathetic nervous system to a lesser extent (ie, manidipine)[89] may have a more favorable adverse event profile.

CCBs differ in their effect on glomerular hemodynamics and urinary albumin excretion.[90] Conventional dihydropyridinic CCBs may cause vasodilation of afferent renal arterioles with little change in the efferent arteriole diameter, and consequently increase intraglomerular pressure and proteinuria; newer dihydropyrinidic CCBs (ie, manidipine, benidipine) are believed to induce vasodilatation not only in the glomerular afferent arteriole, but also in the efferent arteriole, resulting in a reduced proteinuria.[91–93] Non-dihydropyridinic CCBs (ie, verapamil) offer a mild protective effect on proteinuria in diabetic nephropathy, beyond their antihypertensive action.[94] Concerning the renal effects of CCBs in patients with type 2 diabetes and hypertension, it is important to note that all trials directly comparing CCBs and RAS blocking agents (ACE inhibitors or ARBs) showed no difference in the rate of change of GFR.[81] So, even if albuminuria is usually more markedly reduced by ACE inhibitors or ARBs than by CCBs, this does not translate into a greater renoprotection, as expressed by the slope of GFR reduction, but only into greater CV protection.

In light of the above, the combination of an ACE inhibitor with a CCB may offer several advantages (Table 2). First, it obviously provides a consistent and significant addictive effect on BP reduction,[95–103] without affecting lipid and carbohydrate metabolism.[104]

Secondly, ACE inhibitors plus CCBs may have favorable metabolic effects. In hypertensive patients with impaired glucose tolerance, the combination of trandolapril with verapamil

Table 2 Advantages of ACE inhibitor-calcium channel blocker combination therapy

Improved blood pressure control
Favorable metabolic effects
Counterbalances the reflex increase in sympathetic nervous activity induced by calcium channel blockers
Reduced vasodilatory edema
Diuretic and natriuretic effects of calcium channel blockers
Synergistic reduction of proteinuria and the rate of decline in glomerular filtration rate
Increased NO production and decreased cytokine production
Improved fybrinolitic balance
Improved arterial distensibility

reduced the risk of new-onset diabetes, as compared with an angiotensin receptor blocker plus a thiazide diuretic;[105] in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA),[106] an ACE inhibitor/CCB combination lowered the risk of new-onset diabetes by 30%; in addition, type 2 diabetic patients treated with trandolapril plus verapamil had a better glycemic control than those treated with an ACE inhibitor as monotherapy, unrelated to their antihypertensive effect.[107] The metabolic results are even better when new dihydropyridines are combined with ACE inhibitors. A recent trial showed a remarkable 59% increase in insulin sensitivity with the delapril/manidipine fixed combination in obese hypertensives after 24 weeks, while olmesartan/thiazide combination was ineffective.[108] Two mechanisms have been proposed for the reduction of insulin resistance observed with CCBs: first, these drugs produce vasodilation and enhance blood flow to skeletal muscle with consequent increased delivery of insulin and glucose and enhanced non-oxidative pathways of glucose utilization; in addition, CCBs also improve insulin sensitivity at the cellular level by decreasing the cytosolic-free calcium concentrations.[109,110]

Thirdly, systemic vasodilation induced by CCBs (especially dihydropyridines) signals a reflex increase in sympathetic nervous activity, which thereby increases heart rate and enhances renal renin excretion,[111] reducing the hypotensive properties of the drug; these effects may be counterbalanced by RAS blockade. Fourthly, vasodilatory edema that may occur with CCBs is often diminished when an ACE inhibitor is added to the antihypertensive regimen.[112] Fifthly, the diuretic and natriuretic effect of CCBs complements ACE inhibitor therapy much as diuretic therapy does, but makes it possible to control BP without using a diuretic when that is desirable;[113] additionally, ACE inhibitors blunt the stimulation of the renin-angiotensin-aldosterone axis that may result from this diuretic effect. Sixthly, in hypertensive type 2 diabetics, the combination of an ACE inhibitor and a CCB may synergistically reduce proteinuria and the rate of decline in GFR.[114] Finally, ACE inhibitors and CCBs stimulate nitric oxide (NO) production through kinin-dependent mechanisms and significantly decrease levels of all inflammatory markers (tumor necrosis factor-α, interleukin-6, nuclear factor-κB); preclinical evidence suggests that combination therapy has additive effects.[115–117] The mechanisms of vascular damage in diabetic patients are very complex, but excess production of reactive oxygen species, endothelial dysfunction and decreased NO bioavailability play key pathogenic roles. In such patients, the neurohormonal imbalance between angiotensin II and NO associated with endothelial dysfunction may also contribute to inflammation and cardiac remodeling after myocardial ischemia. So, ACE inhibitor/CCB combination therapy may have beneficial effects in the management of cardiac ischemia and left ventricular hypertrophy, by limiting inflammation and restoring neurohormonal balance,[118] as well as on fibrinolytic balance[119] and arterial distensibility.[120,121]

A number of hypertension trials and trials on CV or renal endpoints have compared ACE inhibitor/CCB combination therapy and other drugs/placebo in patients with type 2 diabetes and hypertension.

Hypertension trials

In 1991,[104] in order to assess the efficacy and tolerability of a diuretic-free antihypertensive therapy with an ACE inhibitor and a CCB, 47 type 2 diabetic hypertensives randomly received verapamil or enalapril alone and, if BP remained elevated, both agents combined, over a 30-week period. After 10 weeks of monotherapy, 30 patients obtained a DBP lower than 90 mmHg. In the remaining 17 patients, verapamil/enalapril combination therapy decreased BP from $170 \pm 4/104 \pm 2$ to $152 \pm 4/90 \pm 2$ mmHg ($p < 0.001$). Fasting plasma glucose, glycosylated hemoglobin, serum fructosamine, total lipids, high-density and low-density lipoprotein cholesterol, apolipoproteins A-I and B, creatinine, and urinary albumin-creatinine ratio were not significantly modified, demonstrating that BP can be effectively decreased without adversely affecting carbohydrate and lipid metabolism.

A subsequent small crossover trial in 38 patients with type 2 diabetes and hypertension,[119] assigned to benazepril 10 mg/day, amlodipine 5 mg/day or their combination, showed that combination therapy produced a significantly greater reduction in both SBP and DBP than either drug alone, with a mean decrease in BP of –28.3/–20.5 mmHg ($p < 0.001$ versus placebo; $p < 0.01$ versus benazepril or amlodipine monotherapies). The benazepril/amlodipine combination improved fybrinolytic balance more than the single drugs, due to both the decrease in plasma PAI-1 activity and the increase in t-PA activity. These effects may be of particular importance in diabetic hypertensive patients, who have an impaired fibrinolytic activity, which may contribute to the increased risk of atherosclerosis and its clinical complications.

In the Study of Hypertension and the Efficacy of Lotrel in Diabetes (SHIELD) trial,[122] a randomized, double-blind study, 214 patients with hypertension and type 2 diabetes were assigned to amlodipine/benazepril (5/10 mg) combination therapy or conventional treatment (enalapril 10 mg/day).

If target BP (<130/85 mmHg) was not achieved, study drugs were titrated to 10/20 mg/day or 20 mg/day, respectively. HCTZ was added if target BP was still not reached. Time from baseline to achieve BP < 130/85 mmHg was shorter in the combination arm (5.3 ± 3.1 weeks versus 6.4 ± 3.8 weeks, p = 0.001). At 3 months, 63% of patients in the combination group achieved treatment goal, versus 37% in the conventional treatment group (p = 0.002).

A controlled clinical trial[123] investigated the CCB lercanidipine versus HCTZ as add-on to enalapril monotherapy in diabetic patients (type 1 or 2) with uncontrolled hypertension. 174 subjects were included in a 2-week placebo run-in, followed by 4 weeks on enalapril 20 mg/day. Therefore, 135 non-responders (DBP ≥ 90 mmHg) were randomized to either lercanidipine 10 mg/day or HCTZ 12.5 mg/day. Both add-on therapies reduced DBP to a greater extent than enalapril monotherapy; target BP (130/85 mmHg) was achieved in 30.4% of patients on lercanidipine add-on and in 23.2% of subjects on HCTZ add-on, but the differences between the responder rates in the two treatment groups did not reach statistical significance (p > 0.05). Both combinations were well tolerated.

The Amlodipine in Diabetes (ANDI) trial,[124] a randomized parallel-group trial, investigated BP lowering in 374 patients with type 2 diabetes and hypertension. Subjects not reaching BP goals (<130/80 mmHg) after a 4-week open-label treatment with quinapril 20 mg/day (n = 374) were assigned to either quinapril 40 mg/day (n = 167) or quinapril 20 mg/day plus amlodipine 5 mg/day(n = 62). After 6 weeks of treatment, patients receiving combination therapy had significantly greater reductions in SBP (9.9 ± 1.0 mmHg vs 4.3 ± 1.1 mmHg, p < 0.001) and DBP (6.5 ± 0.6 mmHg vs 2.7 ± 0.6 mmHg, p < 0.001), as compared to quinapril monotherapy. Both treatments were well tolerated, and showed a clinically neutral effect on high-sensitivity C-reactive protein.

The MORE trial[125] investigated the efficacy of the fixed-dose combination of a CCB (manidipine 10 mg/day) and an ACE inhibitor (delapril 30 mg/day), compared with a combination of an ARB (losartan 50 mg/day) and a diuretic (HCTZ 12.5 mg/day), in 314 patients with hypertension and controlled type 2 diabetes (HbA_{1c} ≤ 7.5%). All patients underwent ambulatory BP monitoring at baseline and at the end of treatment. After 12 weeks, mean decreases in 24-hour SBP were −9.3 mmHg in the manidine/delapril arm (n = 80) and −10.7 mmHg in the losartan/HCTZ arm (n = 94), respectively. The mean treatment difference was −1.4 mmHg (95% CI −4.5/−1.8), demonstrating the non-inferiority of the manidipine/delapril combination. A lower percentage of patients with increased HBA1c or requiring additional oral antidiabetic therapy was also observed in the CCB/ACE group. Both treatments were well tolerated and displayed comparable safety profiles.

Cardiovascular endpoints

Few large randomized clinical trials have evaluated the effects of a combination regimen (ACE inhibitor + CCB) on major CV outcomes in patients with both diabetes (mostly type 2) and hypertension.

In the aforementioned FACET trial,[29] 380 type 2 diabetic hypertensives were assigned to open-label therapy with either fosinopril (n = 189) or amlodipine (n = 191). The goal BP was defined as SBP ≤ 140 mmHg and DBP ≤ 90 mmHg. However, if BP was not controlled with monotherapy, the other study drug was added at full dose. Therefore, amlodipine was added in 30.7% of the fosinopril group patients (58/189), and fosinopril was added in 26.2% of the amlodipine group patients. The proportion of patients reaching the combined end point of stroke, acute MI or hospitalized angina was significantly lower in the fosinopril group compared with amlodipine (HR 0.49, 95% CI 0.26–0.95, p = 0.03). In crude analyses according to postrandomization treatment, the patients who received fosinopril only (n = 131), amlodipine only (n = 141) and the combination of fosinopril plus amlodipine (n = 108) experienced 10, 27, and 4 major vascular events, respectively. In the same three groups, the number of patients experiencing acute MI was 7, 13, and 3, respectively; the number of patients with hospitalized angina was 0, 4 and 0; and the number of patients who experienced stroke was 3, 10 and 1, respectively. Compared with amlodipine alone, the combination treatment with fosinopril and amlodipine decreased the risk of major vascular events more than fosinopril only (HR 0.17, 95% CI 0.06–0.5, p = 0.001 versus HR 0.37, 95% CI 0.18–0.77, p = 0.008, respectively). Therefore, combination therapy with ACE inhibitor and CCB scored better than monotherapy, but this important finding was not emphasized by the authors.[81]

In the Hypertension Optimal Treatment (HOT) trial,[126] 18,790 hypertensive patients (DBP between 100 and 115 mmHg) were randomly assigned to different target diastolic BP: ≤ 90 mmHg (n = 6 264), ≤85 mmHg (n = 6264) or ≤80 mmHg (n = 6262). A CCB (felodipine) was given as baseline therapy, with the possible addition of other agents, according to a 5-step regimen. ACE inhibitors were added at step two, and most patients received an ACE inhibitor/CCB combination therapy. In the diabetic cohort of the trial (n = 1501), a decline in the rate of major CV events was observed in relation to the target

group (p = 0.005). In the group randomized to ≤80 mmHg the risk of major CV events was halved in comparison with that of the target group ≤90 mmHg. When silent MI was included, this change was attenuated but remained significant. The approximate halving of the risk was also observed for all MI, although not statistically significant. All stroke also showed a declining rate with lower target BP groups, with a risk reduction of about 30% in the ≤80 mmHg target group vs ≤90 mmHg target group. Cardiovascular mortality was also significantly lower in the ≤80 mmHg target group than in each of the other target groups.

In the diabetic subgroup of the Systolic Hypertension in Europe Trial (492/4695 patients),[127] subjects with diabetes and systolic hypertension were randomly assigned to either active treatment or placebo. Active treatment consisted of a CCB (nitrendipine 10 to 40 mg/day), with the possible addition or substitution of enalapril (5 to 20 mg/day) or HCTZ (12.5 to 25 mg/day) or both, titrated to reduce SBP by at least 20 mmHg and to less than 150 mmHg. Again, the second step was an ACE inhibitor, and most patients received an ACE inhibitor plus CCB combination. At 2 years, active treatment reduced overall mortality by 55% (from 45.1 deaths per 1000 patients to 26.4 deaths per 1000 patients), CV mortality by 76%, all CV events combined by 69%, fatal and non-fatal strokes by 73% and all cardiac events combined by 63%. Reductions in overall mortality, CV mortality and all CV events were significantly larger among the diabetic patients than among the nondiabetics (p = 0.04, p = 0.02, and p = 0.01, respectively).

The International Verapamil-Trandolapril Study (INVEST),[128] a prospective, randomized, open-label, blinded endpoint (PROBE) trial, enrolled 22,576 patients with hypertension and CHD, randomly assigned to a non-dihydropyridine CCB (verapamil SR) or a beta blocker-based (atenolol) regimen, and followed up for a mean duration of 2.7 years. In the diabetic cohort of the trial,[129] 6,400 patients were randomized to 240 mg/day of verapamil SR or 50 mg/day of atenolol, titrated to maximal doses to achieve a target BP of <130/85 mmHg. If BP goal was not achieved, trandolapril and HCTZ were recommended as primary and secondary add-on agents in the verapamil SR group, and the sequence was reversed in the atenolol group. At 24 months, the majority of participants required add-on therapy, with differences in use of trandolapril and HCTZ by strategy. In the verapamil SR group, 72.1% of patients were taking trandolapril and 51.2% HCTZ, versus 64.1% and 62.8% of patients in the atenolol group, respectively. Risk for primary (a composite of death, non-fatal MI or non-fatal stroke) and secondary outcomes (death, non-fatal MI, non-fatal stroke, BP control, CV hospitalizations, and CV death) did not differ by strategy, as well as BP control. Finally, an on-treatment analysis of randomized drugs, using atenolol 50 mg/day as a reference group, indicated a trend for reduced risk of the primary outcome with the addition of 2 mg/day of trandolapril to the verapamil-SR based strategy or of 12.5 mg/day of HCTZ to the atenolol-based strategy. This trial suggested that a combination therapy was more effective for reducing adverse outcomes in diabetic hypertensives, and that an ACE inhibitor/CCB combination could be used as an alternative to a beta-blocker based strategy in patients with concomitant CAD.

In the Bergamo Nephrologic Diabetes Complication (BENEDICT) trial,[130] enrolling 1204 normoalbuminuric patients with type 2 diabetes and hypertension, randomized to trandolapril, verapamil, verapamil plus trandolapril or placebo (see below), the incidence of non-fatal CV events was similar in the four treatment groups (3.7% in the combination group, 4.0% in the trandolapril group, 4.3% in the verapamil group, and 4.0% in the placebo group). One subject receiving trandolapril, 1 receiving verapamil, and 3 receiving placebo died from a CV event. No fatal CV events occurred in the group receiving trandolapril plus verapamil.

The Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA)[106] was designed to compare the effect on non-fatal MI and fatal CHD of two combination strategies, atenolol plus bendroflumethiazide versus amlodipine plus perindopril, in more than 19,000 hypertensive patients with no prior history of CHD. The study population was required to have at least three additional risk factors for CV disease: type 2 diabetes, peripheral arterial disease, previous stroke or transient ischemic attack, microalbuminuria or proteinuria, smoking and so forth. In the diabetic cohort of the trial,[131] 5137 patients were randomized to the atenolol-based regimen (n = 2 572) or to the amlodipine-based regimen (n = 2 565). A majority of patients received combination treatment with either amlodipine and perindopril or atenolol and thiazide, respectively. The mean SBP and DBP throughout the trial were 3.0 and 1.9 mmHg lower in the amlodipine/perindopril arm. In the latter, a significantly lower incidence of total CV events was observed, compared with the atenolol/HCTZ regimen (HR 0.86, 95% CI 0.76–0.98, p = 0.026). Fatal and non-fatal strokes were 25% lower (p = 0.017), peripheral arterial disease 48% lower (p = 0.004) and coronary revascularization procedures 57% lower (p < 0.001) in the amlodipine/perindopril group. However, non-fatal MI and fatal CHD, the primary endpoint

in ASCOT, were reduced by a non-significant 8% (HR 0.92, 95% CI 0.74–1.15, p = 0.46).

The recently published Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial,[132] which included a large population of diabetic patients (see below), indicates that the combination of an ACE inhibitor and a CCB was superior to the combination of an ACE inhibitor and a diuretic in reducing CV endpoints.

Renal endpoints

In a randomized, double-blind, parallel group designed trial,[133] 37 patients with type 2 diabetes, hypertension and urinary protein excretion of >300 mg/day were assigned to verapamil (a non-dihydropyridinic CCB), trandolapril or trandolapril + verapamil. Primary endpoint was a 25% greater reduction in urinary protein excretion (detected using 24-hour urine determinations) in the combination group as compared to either trandolapril or verapamil alone. During the trial, there was a 3 to 4 mmHg lower mean arterial pressure in the combination group versus monotherapy groups. The combination of trandolapril and verapamil produced and sustained a greater reduction in proteinuria (from 1403 to 592 mg/day) compared to higher doses of either verapamil (from 1349 to 985 mg/day) or trandolapril (from 1274 to 840 mg/day), independently of BP reduction ($p < 0.05$).

In a subsequent, larger trial,[134] 309 hypertensive patients with type 2 diabetes and microalbuminuria were randomized to the dihydropyridinic CCB amlodipine (5 to 15 mg/day), the ACE inhibitor fosinopril (10 to 30 mg/day), or both drugs. During the 4 years of follow-up, combination therapy was more effective in reducing BP than either drug alone, without affecting glucose homeostasis. All three treatments resulted in a significant decrease in urinary albumin excretion (UAE), but this effect became evident earlier and was more pronounced in the fosinopril than in the amlodipine arm. Again, combination therapy provided a greater antialbuminuric effect than the single drugs. In addition, a greater percentage of patients in the combination group were non-microalbuminuric at 4 years than in amlodipine or fosinopril groups (67%, 33% and 46%, respectively).

In a 12-week, double-blind SHIELD substudy,[121] 20 patients with hypertension, type 2 diabetes and microalbuminuria were randomized to either a fixed-dose combination of amlodipine and benazapril or to enalapril monotherapy. At week 12, subjects in both the combination and the enalapril group experienced similar reductions from baseline in urinary microalbumin excretion, from 124 ± 91 μg/mg to 36 ± 14 μg/mg creatinine and from 102 ± 58 μg/mg to 27 ± 23 μg/mg creatinine, respectively ($p < 0.01$ for both groups). Patients in both treatment groups demonstrated similar reductions in BP.

In the specific setting of primary prevention of diabetic nephropathy, the Bergamo Nephrologic Diabetes Complication Trial (BENEDICT)[130] was designed to assess whether ACE inhibitors and non-dihydropyridine CCBs, alone or in combination, are able to prevent microalbuminuria in patients with type 2 diabetes, hypertension and normal urinary albumin excretion. 1204 normoalbuminuric patients were randomized to trandolapril (n = 301), verapamil (n = 303), verapamil plus trandolapril (n = 300) or placebo (n = 300). Primary endpoint was the development of persistent microalbuminuria (overnight AER ≥ 20 μg/min at two consecutive visits). Target BP was 120/80 mmHg. As compared with placebo, trandolapril plus verapamil and trandolapril alone decreased the incidence of microalbuminuria to a similar extent. In particular, persistent microalbuminuria developed in 5.7% of patients receiving combination therapy, as compared with 10% of the subjects receiving placebo. In addition, the effects of trandolapril/verapamil and trandolapril in preventing microalbuminuria exceeded expectations based on BP reduction per se. On the other hand, verapamil alone did not significantly delay the onset of microalbuminuria.

In the Add-on manidipine versus amlodipine in diabetic patients with hypertension and microalbuminuria (AMANDHA) trial,[135] 91 diabetic patients with uncontrolled hypertension and microalbuminuria despite full-dose treatment with a renin-angiotensin system blocker were randomized to either manidipine 20 mg/day (n = 61) or amlodipine 10 mg/day (n = 30) in a 2:1 ratio. After 6 months of treatment, patients were monitored for microalbuminuria for additional 18 months. Urinary albumin excretion was reduced by 65.5% with manidipine versus 20% with amlodipine at 6 months ($p < 0.01$), and by 62.7 versus 16.6% ($p < 0.01$) at 24 months, confirming the peculiar effects on glomerular hemodynamics of the latest generation of dihydropyridines.

In conclusion, even if there is sound scientific evidence suggesting the efficacy of ACE inhibitors plus CCBs in reducing proteinuria, the individual role of the two drug classes is still a matter of debate; at least in the case of older dihydropyridines, most of the antiproteinuric effects could be explained by ACE inhibition alone and/or by the additional BP reduction obtained by combination therapy. In any case,

combination therapy with ACE inhibitors and CCBs may reduce the slope of GFR reduction.[114]

Other ACE inhibitor combinations

ACE inhibitor plus angiotensin receptor blocker

The RAS has evolved to play an integral role in the preservation of hemodynamic stability in human beings, by regulating extracellular fluid volume, sodium balance, and CV function through direct and indirect effects on multiple organ systems.[136] Activation of the renin-angiotensin axis produces the biologically active peptide angiotensin II, which has several structural and hemodynamic effects, including stimulation of the sympathetic nervous system, vasoconstriction, increased aldosterone release and sodium retention, cardiac remodeling, smooth muscle cells growth and proliferation, vascular inflammation, generation of reactive oxygen species, endothelial dysfunction, renal fibrosis and so forth. ACE inhibitors and ARBs work at different steps of the RAS. Although ACE inhibitors are able to reduce angiotensin II formation, non-ACE dependent pathways have also been identified.[137] On the other hand, ARBs antagonize the binding of angiotensin II to the AT_1 receptor, which mediates most of the undesirable effects associated with angiotensin II. Each of these drug classes has been shown to be effective in the treatment of congestive heart failure, proteinuric chronic kidney disease (diabetic or not) and high-CV risk patients. For example, the RESOLVD pilot study[138] demonstrated that combining enalapril with candesartan provides superior suppression of left-ventricular remodeling and RAS neurohormones as opposed to either therapy alone. The individual success of ACE inhibitors and ARBs has fueled the theory that combination therapy should provide additional CV and renal protection. The foundation of this premise, although biologically plausible, has yet to be proven in a compelling enough fashion to support the everyday use of these two drug classes in combination. To date, no long-term clinical trials have assessed mortality and morbidity with ACE inhibitor/ARB combination therapy in a population consisting exclusively of type 2 diabetic hypertensives. In the VALsartan In Acute myocardial iNfarcTion trial,[139] 14,703 patients (55.3% hypertensives) with acute MI complicated by heart failure or left ventricular systolic dysfunction or both were randomized to captopril (n = 4909), valsartan (n = 4909) or combination therapy (n = 4885). In the latter arm, there were 1146 (23.5%) diabetic patients (mostly type 2 diabetics, over 70% hypertensives).[140] In these subjects, the combination regimen did not reduce total mortality ($p = 0.7$) or the combined CV endpoint ($p = 0.85$), as compared with captopril monotherapy, despite additional lowering of BP and a clear increase in the rate of intolerance to treatment. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET)[141] enrolled 25 620 patients at high CV risk, randomized to ramipril (n = 8576), telmisartan (n = 8542) or both (n = 8502). 3220 diabetic patients (mostly type 2 diabetics with hypertension) received the combination of the two drugs. Again, combination therapy did not offer an additional reduction in the primary outcome (death from CV causes, MI, stroke, or hospitalization for heart failure; $p = 0.15$), compared with ramipril, but significantly increased the risk of hypotension, syncope, hyperkalemia and renal dysfunction. Similarly, no benefit of combination therapy on the primary renal outcome (dialysis, doubling of serum creatinine, and death) was seen in participants with diabetic nephropathy;[142] in the ONTARGET trial, the only benefit provided by dual RAS blockade was a greater reduction in urinary albumin excretion. This finding is consistent with a recent meta-analysis investigating combination therapy with ACE inhibitors and ARBs for diabetic nephropathy[143], wherein the combination regimen lowered 24-hour proteinuria to a greater extent than either drug as monotherapy, even if the few long-term studies included (12 months)[144,145] had not demonstrated any benefit.

As a consequence, concerns about dual-agent blockade of the RAS have been raised, particularly about the potential increase in the incidence of hyperkalemia and decrease in the GFR, even in the presence of normal renal arteries (late-onset renal failure from angiotensin blockade, LORFFAB).[146,147]

ACE inhibitor plus aliskiren

Aliskiren is a low-molecular-weight hydrophilic non-peptide, which exerts a potent and specific competitive inhibition on renin, the initial and rate-limiting step of the RAS, reducing angiotensin I generation from angiotensinogen.[148] A reactive increase in the activity of the renin occurs when either ACE inhibitors or ARBs are used for long periods. Renin exerts additional actions through a renin receptor, leading to the production of angiotensin and aldosterone. Therefore, the prospect of dual blockade of the RAS with aliskiren and an ACE inhibitor has appeared promising. A phase 3 clinical trial randomized 837 patients with diabetes (mostly type 2 diabetics) and hypertension to aliskiren 150 mg/day alone, ramipril 5 mg/day alone or a combination of aliskiren 150 mg/day and ramipril 5 mg/day.[149] After 4 weeks, the

dose in each arm was doubled for an additional 4 weeks. At 8 weeks, combination therapy was significantly more effective in reducing mean sitting SBP compared with either monotherapy ($p < 0.005$), with an additional BP reduction of 4.6/2.1 mmHg over ramipril monotherapy. Treatments were well tolerated, with adverse events occurring in 33.8%, 32.3% and 30% of patients on ramipril, aliskiren, or aliskiren/ramipril, respectively. Most adverse events were mild or moderate. A substudy in 173 patients who underwent 24-hour BP monitoring at baseline and at the end of the trial[150] showed that adding aliskiren to ramipril improves 24-hour BP control compared with monotherapy in patients with diabetes and hypertension, with a greater reduction in the early morning BP surge (21–24 hours post dose), which is associated with an increased CV risk.

ACE inhibitor plus α-adrenergic blocker

In a small crossover trial,[151] 76 patients with type 2 diabetes, hypertension and albuminuria were randomized to receive the ACE inhibitor cilazapril (2.5–10 mg/day), the α-adrenergic blocker doxazosin (2–8 mg/day) or both drugs at half doses. Patients of the first two groups received a single agent for 4 months, the drugs were then crossed for an additional 4 months followed by the addition of HCTZ for a final 4-month period. Patients of the cilazapril/doxazosin group received both drugs for 4 months, then HCTZ was added for an additional 4 months. All three initial regimens resulted in significant decline in both SBP and DBP values ($p < 0.001$). The combination of cilazapril with doxazosin had a significant greater antialbuminuric effect: albuminuria decreased from 365 ± 115 to 162 ± 105 mg/24 hours, an RR of 56% (95% CI 16%–88%; $p = 0.001$), as compared with 350 ± 105 down to 205 ± 96 mg/24 hours in the cilazapril group and with 373 ± 121 down to 322 ± 107 mg/24 hours in the doxazosin group. In the combination arm, the addition of HCTZ was followed by a further decline in albuminuria.

Which is the "best" ACE inhibitor combination in hypertensive patients with type 2 diabetes? Update after the GUARD and ACCOMPLISH trials

Two recently published trials, GUARD and ACCOMPLISH, may help to shed a new light on this area. They are the first clinical studies specifically designed to directly compare initial combination therapy of either ACE inhibitor and diuretic or ACE inhibitor and CCB. In the Gauging Albuminuria Reduction with Lotrel in Diabetic Patients with Hypertension (GUARD) trial,[114] 332 hypertensive, albuminuric type 2 diabetics were assigned to benazepril/amlodipine or benazepril/HCTZ. After 1 year of treatment, both combinations significantly reduced the urinary albumin to creatinine ratio and the sitting BP. However, while BP was reduced more by the combination ACE inhibitor/CCB, initial treatment with benazepril and HCTZ resulted in a greater reduction in albuminuria, compared with benazepril plus amlodipine. The reasons for this difference could be multiple. First, conventional dihydropyridinic CCBs, such as amlodipine, may cause vasodilation of afferent renal arterioles with minor changes in the efferent arteriole diameter, with a consequent increase in intraglomerular pressure and proteinuria. Therefore, the observations of the GUARD cannot be extended to other dihydropyridinic (ie, manidipine) or non-dihydropyridinic CCBs, as clearly showed by the recently published AMANDHA trial.[135] Other possible explanations suggested by the authors of the trial include greater reduction in eGFR in the diuretic group as well as differences in preexisting volume status. Finally, high sodium intake may blunt the antiproteinuric effects of ACE inhibitors; in such patients, the use of thiazide diuretics may overcome this blunting effect. However, another recently published trial in hypertensive patients with type 2 diabetes[152] showed that adding manidipine on top of RAS blocker, candesartan, reduced the urinary albumin excretion by 53%, while thiazide diuretic add-on was ineffective. Altough obtained with a combination therapy based on an angiotensin receptor blocker instead of an ACE inhibitor, these results are in sharp contrast with the discussed GUARD trial.

Interestingly, rates of progression to overt diabetic nephropathy by the end of the GUARD trial were similar between the benazepril/amlodipine and the benazepril/hydrochlorotiazide group (4.6% vs 4.0%, $p = 0.79$). More importantly, the mean decrease in the estimated GFR (eGFR) over the 52-week period was less in the benazepril/amlodipine group than in the benazepril/HCTZ group (−2.03 ± 1 4.2 vs −13.64 ± 16.1 mL/min, $p < 0.0001$). Again, a greater reduction in proteinuria, as observed in the benazepril/HCTZ arm of GUARD, does not necessarily translate into greater renoprotection, as expressed by the slope of GFR reduction.

Further in favor of the ACE inhibitor/CCB combination, the recently published ACCOMPLISH trial[132] demonstrated a striking superiority of the benazepril/amlodipine combination, as compared with benazepril/HCTZ, in reducing CV events in 11,506 hypertensive patients at high CV risk, 60% of

whom were diabetics. After a mean of 30 months of treatment exposure, the primary outcome, which was defined as the composite of a CV event and death from CV causes, occurred in 552 patients (9.6%) in the benazepril/amlodipine group as compared with 679 patients (11.8%) in the benazepril/HCTZ group (HR 0.80, $p < 0.001$). For the secondary endpoint of death from CV causes plus nonfatal MI and non-fatal stroke, there were 288 events (5%) in the first group as compared with 364 (6.3%) in the second group (HR 0.79, $p = 0.002$); similarly, for the secondary endpoint of CV events, there were 494 events (8.6%) in the benazepril/amlodipine arm versus 592 (10.3%) in the benazepril/HCTZ arm (HR 0.83, $p = 0.002$).

In conclusion, emerging evidence strongly supports the use of an ACE inhibitor/CCB combination in high-risk patients. Because more than 75% of hypertensive patients with type 2 diabetes will require a combination therapy to adequately control BP,[17,153] an ACE inhibitor/CCB association may be the first choice for controlling BP in hypertensive patients with type 2 diabetes, providing at the same time both reno- and cardioprotection.

Disclosures

The authors disclose no conflicts of interest.

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