

Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers in preventive cardiology: which drug to use and what to expect in light of the ONTARGET trial

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The recently reported ONTARGET trial [1] has yielded important new information on the comparative benefits of the angiotensin-converting enzyme inhibitor ramipril and the angiotensin receptor blocker telmisartan among patients at relatively high risk of atherosclerotic events, but free of heart failure. The results have significant implications for the clinical management of such patients.

Excessive activity of the renal-angiotensin-aldosterone system (RAAS) is a key contributor to the etiology of arterial hypertension. The juxtaglomerular cells of the renal afferent arteriole release renin in response to decreased perfusion pressure. Renin acts on its substrate angiotensinogen (a circulating globulin synthesized in the liver) to yield the decapeptide angiotensin I, which in turn is enzymatically cleaved to the octapeptide angiotensin II by the action of angiotensin-converting enzyme (ACE), found primarily in pulmonary vascular endothelium. Angiotensin II acts on a wide range of tissues, primarily via the AT_1 receptor, although some of these actions may be opposed by its stimulation of the AT_2 receptor. Angiotensin II is a vasopressor which acts by directly constricting arterioles and stimulating the synthesis of aldosterone by the adrenal cortex. In situ synthesis of angiotensin II occurs in many tissues, including endothelium, brain, heart and adrenal cortex. Whether synthesized in the circulation following renal release of renin, or synthesized in situ, angiotensin II has additional potentially deleterious actions on vascular endothelium (oxidative stress, endothelial dysfunction, atherosclerosis, plaque rupture), myocardium (apoptosis, remodeling, fibrosis), glomerulus (inflammation, fibrosis), and tissue insulin responsiveness [2]. Excessive stimulation of AT_1 receptors can contribute to the development not only of hypertension,

but also of acute coronary syndromes, myocardial hypertrophy, dysfunction and dilation, stroke, proteinuria, renal failure and diabetes mellitus. Therapeutic blockade of the RAAS was first achieved with the angiotensin-converting enzyme inhibitors (ACEI). These agents block the action of ACE, but not of alternative enzymatic pathways, such as those of chymase and serum proteases [3]. More recently, angiotensin receptor blockers (ARBs) have been developed to block AT_1 receptors, which mediate the potentially deleterious actions of angiotensin II, whatever its source. Angiotensin-converting enzyme is also responsible for the breakdown of bradykinin, elevated levels of which result from ACEI therapy. Although elevated bradykinin likely accounts for the relatively common ACEI side effect of cough and plays a role in the uncommon complication of angioedema, this polypeptide has potentially beneficial vasodilator, cardioprotective and antihypertrophic effects which may be accentuated with ACEI therapy and contribute to its efficacy [3].

In multiple trials among patients with arterial hypertension, ACEI were shown to be efficacious in lowering blood pressure [4], and also in reducing all cause and cardiovascular mortality, stroke and renal disease [4-6]. These observations in hypertensive patients led to studies which demonstrated reductions of mortality and progression of heart failure in patients with clinical heart failure [7,8] and of the composite outcome of death or heart failure in those with decreased left ventricular ejection fraction (LVEF) in the absence of clinical heart failure [9]. Subsequently, a series of short term trials in acute myocardial infarction demonstrated modest efficacy, with a meta-analysis indicating a statistically significant 7% reduction in 30-day mortality [10]. Several trials of longer term therapy following acute myocardial infarction showed marked efficacy in the settings of clinical heart failure [11], clinical heart failure or left ventricular dysfunction [12], or simply reduced LVEF but no clinical heart failure [13]. The observation of a reduced incidence of myocardial infarction and acute coronary syndromes in patients randomized in trials of heart failure as well as accumulating evidence for

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effects of angiotensin II on myocardial hypertrophy and endothelial dysfunction [14], led to the design of the HOPE trial [15]. The study subjects were at relatively high risk of atherosclerotic events (history of coronary artery disease, stroke, peripheral vascular disease or diabetes plus one additional cardiovascular risk factor) but were not known to have a low ejection fraction or heart failure. They were randomly allocated, double blind, to ramipril 10 mg/24 h or placebo and followed for a mean of five years. Ramipril significantly reduced the incidence of the composite outcome of myocardial infarction, stroke or cardiovascular death (relative risk [RR] 0.78), as well as a range of specific outcomes including death from any cause (RR 0.84), cardiovascular death (RR 0.74), myocardial infarction (RR 0.80), stroke (RR 0.68), complications related to diabetes (RR 0.84) and new diagnosis of diabetes (RR 0.66). Similar results were found in the EUROPA trial [16] of perindopril vs. placebo. Although the PEACE trial [17] of trandolapril vs. placebo found only a statistically insignificant reduction of the principal outcome (HR 0.96), an overview of the three trials showed a significant reduction, with no significant heterogeneity among the trials [18].

The alternative pathways for the conversion of angiotensin I to angiotensin II which are not inhibited by ACEI constitute a potential limitation to their efficacy. Patients on prolonged therapy with an ACEI are found to have serum levels of angiotensin II which approach those prior to institution of therapy, and in addition it has been shown that myocardial angiotensin II synthesis continues in the presence of ACEI therapy [2]. The well-recognized side effect of dry cough occurs relatively frequently with ACEI, and the potentially life-threatening problem of angioedema is occasionally observed. Accordingly there was a strong rationale for the development of direct inhibitors of the angiotensin II receptor. These agents are as effective as ACEI for the control of hypertension [4,19], although there is a paucity of long term data on the comparative efficacy for the reduction of major clinical outcomes, including death, myocardial infarction and stroke [19]. In patients with chronic heart failure, the ARBs have been compared to placebo in CHARM-Alternative [20] and several smaller trials and a meta-analysis [21] has shown reduced all-cause mortality (OR 0.83) and heart failure hospitalizations (OR 0.64). ARBs have also been directly compared to ACEI in ELITE [22], ELITE II [23] and several smaller trials and a meta-analysis [21] has shown no significant differences in the outcomes of all-cause mortality (OR 1.06) or heart failure hospitalizations (OR 0.95). ARBs have also been compared to ACEI in the setting of acute myocardial infarction and heart failure. No significant differences in all-cause mortality or heart failure hospitalizations were found between losartan and captopril in OPTIMAAL [24] or between valsartan and captopril in VALIANT [25]. ARBs had not been compared to ACEI in a population similar to that of the HOPE trial, prior to the conduct of the ONTARGET trial.

There are several mechanisms by which the combination of an ACEI plus an ARB might offer greater efficacy than ei-

ther agent alone. It is conceivable that more marked vasodilatation or reduction in the tissue effects of angiotensin II might be achieved by the combination, with the additional benefit of elevated levels of bradykinin [2]. In ValHeFT [26], among patients with chronic heart failure, valsartan plus an ACEI vs. ACEI alone significantly reduced the incidence of the combined end point of mortality and morbidity. In the CHARM-Added trial [27], among patients with chronic heart failure and reduced LV function, candesartan plus an ACEI vs. ACEI significantly reduced the incidence of the composite outcome of cardiovascular death or hospital admission for heart failure (hazard ratio [HR] 0.85, $p = 0.011$). In VALIANT [25], among patients with heart failure complicating acute myocardial infarction, the combination of valsartan and captopril was no more effective than captopril alone in reducing the incidence of all-cause mortality (HR 0.98, $p = 0.73$), but it increased the incidence of adverse events.

The ONTARGET trial [1,28] was designed to compare the efficacies of ramipril (an ACEI), telmisartan (an ARB), and their combination in a population of patients free of clinical heart failure or known reduced ejection fraction, who were at relatively high risk of atherosclerotic outcomes. They were being treated with current evidence-based therapies (including statins in 61.6%, β -blockers in 56.9% and antiplatelet agents in 80.9%) and were selected to be similar to that studied in the HOPE trial. A non-inferiority comparison of ARB vs. ACEI was undertaken to determine whether telmisartan would provide protection against atherosclerotic outcomes equivalent to that of ramipril and therefore be a suitable alternative for patients intolerant of ACEI therapy. It was also postulated that the theoretical advantages of an ARB over an ACEI (complete blockade of angiotensin II effects and possibly better tolerance and therefore compliance) might translate into greater overall effectiveness, to be assessed by a superiority comparison if non-inferiority were to be proven. A superiority comparison was designed to determine whether of the combination of ARB + ACEI might offer therapeutic advantages over either agent alone, possibly as a result of complete blockade of angiotensin II (by the ARB) plus the augmentation of bradykinin (by the ACEI).

A total of 25,577 patients were followed for a median of 56 months, with very high levels of compliance with the study drugs. The primary composite outcome of cardiovascular death, myocardial infarction, stroke or hospitalization for heart failure was not different between the telmisartan and ramipril groups (RR 1.01, 95% CI 0.94–1.09). The upper boundary of the 97.5% confidence interval for the RR was less than the pre-set non-inferiority margin (1.13), indicating that telmisartan is non-inferior to ramipril ($p = 0.004$), and preserves about 95% of ramipril's benefit over placebo. There were no significant differences in the incidence of any of the individual components of the composite outcome. The RR for the composite outcome for combination therapy vs. ramipril was 0.99 (95% CI 0.92–1.07). In both the telm-

isartan vs. ramipril and the combination vs. ramipril comparisons the observed relative risks were found to be consistent across a range of subgroups including presence or absence of cardiovascular disease and diabetes, systolic blood pressures, HOPE risk scores, age and sex.

Telmisartan was discontinued less often than ramipril (23% vs. 24.5%, RR 0.94, $p = 0.02$), especially for cough (1.1 vs. 4.5%, RR 0.26, $p < 0.001$) and for angioedema (0.1 vs. 0.3%, RR 0.4, $p = 0.01$). Telmisartan was more often discontinued for hypotensive symptoms (2.7 vs. 1.7%, RR 1.54, $p < 0.001$). The combination was discontinued significantly more frequently than ramipril for hypertensive symptoms, syncope, diarrhea and renal impairment.

The failure of combination therapy in ONTARGET, to offer any advantage over ramipril alone, was consistent with the results of combination therapy in the VALIANT study [25] of valsartan and captopril in patients with heart failure relatively early following myocardial infarction. In that trial, valsartan was equivalent to captopril, while the combination offered no additional benefit over either agent alone. On the other hand, the ONTARGET results for combination therapy are to some extent at variance with two recent studies [26,27] and an overview [21]. In ValHeFT [26], the addition of valsartan to various ACEI reduced the composite of mortality and morbidity, while in CHARM-Added [27], the addition of candesartan to various ACEI reduced the composite outcome of cardiovascular death or hospitalization for heart failure. However, the designs of these trials differed importantly from that of ONTARGET in that they enrolled patients with heart failure that was not fully controlled on ACEI, and the ACEI therapy was not governed by the study protocols but by physician choice and was likely not at appropriate maximum dose. The increase in withdrawals from therapy and of side effects (renal dysfunction, hyperkalemia, symptomatic hypotension) observed with combination therapy in ONTARGET was consistent with the results of an overview of four previous trials of combination ACEI and ARB

therapy in patients with heart failure, either chronic or complicating acute myocardial infarction [29].

What is the clinical importance of the findings from the ONTARGET trial? First of all, telmisartan has been convincingly demonstrated to be equivalent to ramipril for the prevention of important vascular outcomes in a population of patients at relatively high risk but free of known heart failure. When initiating blockade of the RAAS in such patients, physicians now have a choice of equivalently effective therapies, and must weigh factors such as slightly differing side effects profiles and cost in making the choice. ONTARGET has provided quantitative comparisons between ramipril and telmisartan of the frequencies of cough, angioedema and hypotensive symptoms. Telmisartan rather than ramipril should be prescribed for patients who are intolerant of ACEI. Whether or not the benefit of telmisartan is a class effect or drug specific is uncertain, but for the present this agent would be the ARB of choice in this population. Finally, ONTARGET has shown that in this population of patients who are at high risk of atherosclerotic events but are free of heart failure, the theoretically attractive combination of an ACEI and an ARB confers no advantage over either agent alone and causes more side effects.

REFERENCES

1. The ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008; 358: 1547-1559.
2. Unger T, Stoppelhaar M. Rationale for double renin-angiotensin-aldosterone system blockade. *Am J Cardiol*. 2007; 100: 25J-31J.
3. Urata H, Healy B, Stewart RW, et al. Angiotensin II-forming pathways in normal and failing human hearts. *Circ Res*. 1990; 66: 883-890.
4. Chobanian AV, Bakris GL, Black HR, et al. National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003; 289: 2560-2572.
5. Psaty BM, Lumley T, Furberg CD, et al. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. *JAMA* 2003; 289: 2534-2544.

From the Editor

Synopsis: The ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008; 358: 1547-1559.

In this double blind randomized controlled trial 25,620 patients at high risk for vascular events (patients with cardiovascular disease or diabetes with end-organ damage, without symptomatic heart failure) were allocated into 3 groups receiving 80 mg of telmisartan per day, 10 mg of ramipril per day or both drugs. At a median follow-up of 4.5 years it has been found that telmisartan is as effective as ramipril in cardiovascular prevention (a composite outcome of cardiovascular death, myocardial infarction, stroke and hospitalization for heart failure. Less patients in the telmisartan group than in the ramipril group discontinued therapy because of cough (NNT 33) and angioedema (NNT 574), but more because of hypotension (NNH 106). The combined therapy did not have more beneficial effect on cardiovascular events than ramipril alone and was more often discontinued because of renal dysfunction (NNH 250), hypotension (NNH 33), syncope (NNH 600) and diarrhea (NNH 314).

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EDITORIALS

6. Turnbull F. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet*. 2003; 362: 1527-1535.
7. The CONSENSUS trial study group. Effects of enalapril on mortality in severe congestive heart failure; results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med*. 1987; 316: 1429-1435.
8. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med*. 1991; 325: 293-302.
9. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med*. 1992; 327: 685-691.
10. ACE Inhibitor Myocardial Infarction Collaborative Group. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100 000 patients in randomized trials. *Circulation*. 1998; 97: 2202-2212.
11. Pfeffer MA, Braunwald E, Moyé LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement trial. *N Engl J Med*. 1992; 327: 669-677.
12. Kober L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 1995; 333: 1670-1676.
13. Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet*. 1993; 342: 821-828.
14. Lonn EM, Yusuf S, Jha P, et al. Emerging role of angiotensin-converting enzyme inhibitors in cardiac and vascular protection. *Circulation*. 1993; 90: 2056-2069.
15. Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med*. 2000; 342: 145-153.
16. The European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomized, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet*. 2003; 362: 782-788.
17. The PEACE Trial Investigators. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med*. 2004; 351: 2058-2068.
18. Dagenais GR, Pogue J, Fox K, et al. Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. *Lancet*. 2006; 368: 581-588.
19. Matchar DB, McCrory DC, Orlando LA, et al. Systematic review: comparative effectiveness of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers for treating essential hypertension. *Ann Intern Med*. 2008; 148: 16-29.
20. Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet*. 2003; 362: 772-776.
21. Lee VC, Rhew DC, Dylan M, Badamgarav E, Braunstein GD, Weingarten SR. Meta-analysis: Angiotensin-receptor blockers in chronic heart failure and high-risk acute myocardial infarction. *Ann Int Med* 2004; 141: 693-704.
22. Pitt B, Segal R, Martinez FA, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet*. 1997; 349: 747-752.
23. Pitt B, Poole-Wilson PA, Segal R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial – the Losartan Heart Failure Survival Study ELITE II. *Lancet*. 2000; 355: 1582-1587.
24. Dickstein K, Kjekshus J. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial, Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. *Lancet*. 2002; 360: 752-760.
25. Pfeffer MA, McMurray JJV, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med*. 2003; 349: 1893-1906.
26. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med*. 2001; 345: 1667-1675.
27. McMurray JJ, Ostergren J, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet*. 2003; 362: 767-771.
28. Teo K, Yusuf S, Sleight P, et al. Rationale, design, and baseline characteristics of 2 large, simple, randomized trials evaluating telmisartan, ramipril, and their combination in high-risk patients: the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (ONTARGET/TRANSCEND) trials. *Am Heart J*. 2004; 148: 52-61.
29. Phillips CO, Kashani A, Ko DK, et al. Adverse effects of combination angiotensin II receptor blockers plus angiotensin-converting enzyme inhibitors for left ventricular dysfunction: a quantitative review of data from randomized clinical trials. *Arch Intern Med*. 2007; 167: 1930-1936.