EDITORIAL

Angiotensin-receptor blockers in prevention of cardiovascular events: are they as effective as angiotensin-converting enzyme inhibitors?

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Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) benefit individuals by modulating the renin-angiotensin system (RAS).[1-10] In patients with vascular disease or high risk diabetes without heart failure and in individuals with left ventricular dysfunction with or without heart failure, ACE inhibitors reduce cardiovascular mortality and morbidity.[1-6,9] ARBs have been shown to reduce death or hospitalization for heart failure in patients with heart failure, and also reduce vascular events in high risk subjects with hypertension and left ventricular hypertrophy.[7,8,10] The role of ARBs in preventing cardiovascular events in other high risk individuals has remained unclear until recently when further information became available from results from recent large studies.

It is believed that RAS blockade using either agent alone is incomplete due to escape mechanisms in the production of angiotensin II with the use of ACE inhibitors or reflex increases in angiotensin II levels in the case of ARBs.[11] It has been hypothesized that more complete inhibition of the RAS by combining an ACE inhibitor and an ARB may be more beneficial than using either therapy alone. Furthermore, intolerance to ACE inhibitors is common, and up to 20–30% of individuals cannot tolerate these agents, commonly because of cough but also from other less common adverse effects such as angioedema or renal dysfunction. These issues were addressed in the ONTARGET/TRANSCEND program.[12] The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) compared the effects of the ARB telmisartan, the ACE inhibitor, ramipril, and the combination of the two drugs in patients with vascular disease or high risk diabetes without heart failure.[12,13] The Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) evaluated the effects of telmisartan compared with placebo in these high risk ACE inhibitor intolerant patients.[14]

The design of these trials was based on that of the Heart Outcomes Prevention Evaluation (HOPE) trial which demonstrated that the ACE inhibitor, ramipril was effective in reducing cardiovascular events in high risk individuals with a history of coronary artery disease, cerebrovascular disease, peripheral artery disease or high risk diabetes.[4] These entry criteria were followed in ONTARGET/TRANSCEND, which, however, further defined high risk diabetes as the presence of end organ damage, unlike HOPE which only required the presence of at least one other cardiovascular risk factor. A total of 25,620 eligible patients were enrolled into ONTARGET, 8,576 to ramipril alone, 8542 to telmisartan alone and 8,502 to the combination of ramipril plus telmisartan. In TRANSCEND, 5,926 patients were enrolled, 2,954 to telmisartan and 2,972 to placebo. In both trials, following a 4 week run-in, patients were rapidly up-titrated to the protocol mandated doses, telmisartan 80 mg daily (both in ONTARGET and TRANSCEND), ramipril 10 mg daily, and telmisartan 80 mg plus ramipril 10 mg daily in the combination. Average follow-up in both trials was 56 months. Adherence to the study drugs in these long term trials was high in all treatment arms during the trials.

Telmisartan was well tolerated in both ONTARGET and TRANSCEND. Compared to ramipril, symptomatic hypotension was significantly more frequent with telmisartan but there was no difference in serious adverse events such as syncope, and there was significantly less incidence of angioedema. There was no excess in adverse events with telmisartan when compared to placebo in TRANSCEND. Combination therapy, on the other hand, was associated with excesses in

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TABLE Summary of main outcomes from the trials

	Odds Ratio/Risk Ratios (95% CI)	p
ONTARGET[13]		
Telmisartan vs. Ramipril		
Primary outcome[a]	(0.94–1.09)	0.003[c]
HOPE outcome[b]	0.99 (0.91–1.07)	<0.001[c]
Combination vs. Ramipril		
Primary outcome[a]	0.99 (0.92–1.07)	NS
HOPE outcome[b]	1.00 (0.93–1.09)	NS
TRANSCEND[14]		
Telmisartan vs. Placebo		
Primary outcome[a]	0.92 (0.81–1.05)	0.216
HOPE outcome[b]	0.87 (0.76–1.00)	0.048
HOPE[4] (Ramipril vs. Placebo)[b]	0.78 (0.70–0.86)	<0.001
PRoFESS[16]		
Primary outcome[a]	0.93 (0.86–1.01)	0.067
HOPE outcome[b]	0.93 (0.86–1.01)	0.086
Meta-analysis of TRANSCEND and PRoFESS (Telmisartan vs. Placebo)[14]		
Primary outcome[a]	0.93 (0.86–0.99)	0.026
HOPE outcome[b]	0.91 (0.85–0.98)	0.013
<6 months		
Primary outcome[a]	1.12 (0.99–1.27)	0.075
HOPE outcome[b]	1.13 (0.99–1.28)	0.074
>6 months		
Primary outcome[a]	0.86 (0.80–0.94)	<0.001
HOPE outcome[b]	0.85 (0.78–0.92)	<0.001

a composite of cardiovascular death, myocardial infarction stroke and heart failure hospitalization
b composite of cardiovascular death, myocardial infarction and stroke
c test for non-inferiority
Abbreviations: NS – not significant

symptomatic hypotension, syncope, diarrhea and renal impairment.

In ONTARGET, the primary outcome of cardiovascular death, myocardial infarction, stroke and heart failure hospitalization occurred in 16.5% patients in the ramipril group, 16.7% in the telmisartan group and 16.3% in the combination group. Comparing telmisartan vs. ramipril as per protocol pre-specified non-inferiority hypothesis, telmisartan was found to be non-inferior to, i.e., equivalent or as good as, ramipril in preventing cardiovascular events in high risk subjects (see TABLE) A similar significant finding was made with the major secondary or HOPE study outcome of cardiovascular death, myocardial infarction and stroke. When compared with ramipril, combination therapy did not show an increase in benefits as there were no differences in the primary outcome or secondary HOPE study outcome (TABLE), but this was associated with more adverse events (TABLE).

In TRANSCEND, the primary outcome of cardiovascular death, myocardial infarction, stroke and heart failure hospitalization occurred in 15.7% of patients randomized to telmisartan and 17.0% in the placebo group. The difference was a non-significant relative risk reduction of 8% (p = 0.216). In patients on telmisartan, there was a 13% relative risk reduction (p = 0.048) with 13.0% of these patient having had the secondary HOPE study outcome of cardiovascular death, myocardial infarction and stroke vs. 14.8% in the placebo group. Telmisartan was very well tolerated, with fewer people having had to discontinue the study telmisartan compared to placebo. Hypotensive symptoms, though infrequent, were the most common reasons for permanently discontinuing the telmisartan (0.98%) vs. placebo (0.54%).

By showing that telmisartan is as good as ramipril, one can conclude that that the ARB, telmisartan is effective in preventing cardiovascular events in high risk individuals. It is also clear that combination therapy of the ACE inhibitor ramipril and ARB telmisartan does not increase the expected benefit but instead was associated with significantly excess adverse events, and thus is not recommended. On TRANSCEND, if one were to examine the results on its own, one may be concerned about the modest benefit with telmisartan compared to placebo, in contrast to the conclusive results in ONTARGET or HOPE.

In TRANSCEND, since there was a reduction in the primary outcome of cardiovascular death, myocardial infarction, stroke and heart failure hospitalization in the telmisartan group compared to placebo although the difference was not significant, one may ask whether telmisartan is not effective for this purpose or the conditions for the trial, which were based on HOPE, had changed. The HOPE trial was completed nearly 10 years previously and the population in TRANSCEND could be at lower risk compared to those in HOPE as a result of advances in background therapy. It is also possible that TRANSCEND differed systematically from ONTARGET and previous trials. There are some obvious differences. There were more women in TRANSCEND (40%) than in HOPE and ONTARGET (both 27%). Stain use was much higher in TRANSCEND than in HOPE. There were higher proportions of placebo patients who received β-blockers, calcium channel blockers and diuretics in the placebo group than in the telmisartan group after randomization[14] which may have masked heart failure in the placebo group and reduce the intergroup difference, and this may explain the finding that telmisartan did not have an effect on heart failure. Other trials have shown that ARB do reduce hospitalization for heart failure but these studies were carried out in patients with low ejection fractions and symptomatic heart failure[7-9] (which was excluded in ONTARGET and TRANSCEND), or in those with severe hypertension and left ventricular dysfunction[10]. It is also possible that the risk of heart failure in patients in TRANSCEND had been too low for a benefit to be clearly shown due to entry criteria and background therapy during the study. Thus, telmisartan was associated with a reduction in the secondary HOPE outcome of cardiovascular death, myocardial infarction and stroke, which did not include heart failure hospitalization, compared to placebo.

The lack of an effect on heart failure was also noted in the recent Prevention Regimen For Effectively avoiding Second Strokes (PRoFESS) trial which compared telmisartan with placebo over a shorter period of 2.5 years in patients with a recent stroke, and which also reported a trend towards a reduction in cardiovascular death, myocardial infarction and stroke. When the results of TRANSCEND and PRoFESS were combined in a meta-analysis, there was a highly significant reduction in this composite outcome. When stratified by time, telmisartan had no effect on the composite of cardiovascular death, myocardial infarction and stroke in both trials during the first 6 months but there was a clear benefit after 6 months (**TABLE**).

The question of whether an ARB such as telmisartan is effective in preventing cardiovascular events should be addressed by examining the totality of the available data. The robust data from ONTARGET indicate that telmisartan is as good as ramipril. This finding is reinforced by similar results from the Valsartan in Acute Myocardial Infarction Trial (VALIANT), which combined the effects of an ARB valsartan, an ACE inhibitor captopril and a combination of the two drugs in patients who suffered from an acute myocardial infarction and complicated by left ventricular dysfunction and/or heart failure. The results also showed that valsartan was non-inferior to captopril and that the combination did not have any added benefit but was instead associated with excess, mainly hypotension and renal, adverse events.

The results of TRANSCEND, while somewhat more modest, are consistent with those of the HOPE trial (**TABLE**). It can be speculated whether more prolonged treatment with telmisartan may lead to a larger benefit. Observation of many ACE inhibitors, lipid lowering and blood pressure lowering trials suggests that that little or no benefit could be seen in the early 6 to 12 months and that benefits may emerge later. This lag could be explained by the time needed to modify the disease process by the active treatment. With improvements in background therapies such as increased use of statins and blood pressure lowering agents, the benefits of an additional new agent may be more modest or likely to take longer to emerge. These considerations, and other reasons, may explain the more modest benefits found in TRANSCEND, as compared to HOPE.

The data so far suggest that an ARB such as telmisartan is as effective as the ACE inhibitor ramipril in preventing cardiovascular events in high risk individuals and can be an option for both the physician and patient. The benefits may be somewhat modest, because these patients are likely to be receiving other risk reducing medications such statins, β-blockers and anti-platelet agents, In those individuals who are intolerant to ACE inhibitors, an ARB such as telmisartan should be used for the purpose of preventing cardiovascular events. The combination of an ACE inhibitor and ARB is not recommended for routine secondary prevention.

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