A Perspective on Telmisartan and Cardiovascular Risk

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The angiotensin receptor blockers (ARBs) are well established as safe and effective in the treatment of arterial hypertension. Telmisartan is an ARB with potent blood-pressure–lowering effects. It has a long terminal half-life of about 24 hours (the longest of any of the ARBs), which enables it to sustain blood pressure reductions in the early morning hours, after the previous morning dosing. Unlike the angiotensin-converting enzyme (ACE) inhibitors, the ARBs have not been shown to reduce mortality and morbidity in high-risk patients with coronary disease, peripheral vascular disease, cerebrovascular disease, or diabetes with cardiovascular risk factors without evidence of heart failure or low ejection fraction. Two studies, the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) and the Telmisartan Randomized AssessmeNt Study in ACE-I INtolerant Subjects with Cardiovascular Disease (TRANSCEND) trial, are examining the benefits of ARBs alone and in combination with ACE inhibitors in high-risk patients.
[Rev Cardiovasc Med. *2007;8(3):154-159*]

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Key words: Cardiovascular risk • Angiotensin receptor blockers • Angiotensin-converting enzyme • Telmisartan

Telmisartan is a long-acting angiotensin II type 1 (AT_1) receptor blocker (ARB) that is approved for the treatment of hypertension. As a class, the ARBs have enjoyed a dramatic increase in utilization for the treatment of hypertension and have been shown to be effective in reducing systemic arterial blood pressure. The ARBs have been remarkably free of dose-related adverse events, with a profile that resembles placebo.

It has been recognized that dysregulation of the renin-angiotensin system may play a role in the pathophysiology of many cardiovascular and renal disease

states, such as heart failure, left ventricular dysfunction, the period after myocardial infarction, and proteinuric kidney disease.[1,2] For these reasons, many clinical trials have been implemented over the past decade to assess the effectiveness of the ARBs in various cardiovascular disease states in addition to hypertension (Figure 1). In this regard, the ARB trials resemble the clinical trial development of the angiotensin-converting enzyme (ACE) inhibitors (Figure 2).

The Phenotype of Increased Cardiovascular Risk

The success of the ACE inhibitors and ARBs in various cardiovascular disease states led inexorably to a trial in subjects at high risk for increased cardiovascular morbidity and mor-

tality. Some of the clinical characteristics that define individuals at increased cardiovascular risk are listed in Table 1.[3]

Recently, "traditional" risk factors have been shown to be as predictive as some of the "emerging" biomarkers, such as high-sensitivity C-reactive protein, brain natriuretic peptide, plasma renin activity, plasma homocysteine concentration, and microalbuminuria.[4] It is abundantly clear that risk factors interact to markedly increase cardiovascular risk.

Circadian Influence on Cardiovascular Risk

The risk of many major cardiovascular events, such as myocardial infarction, stroke, and sudden cardiac death, is increased during the early
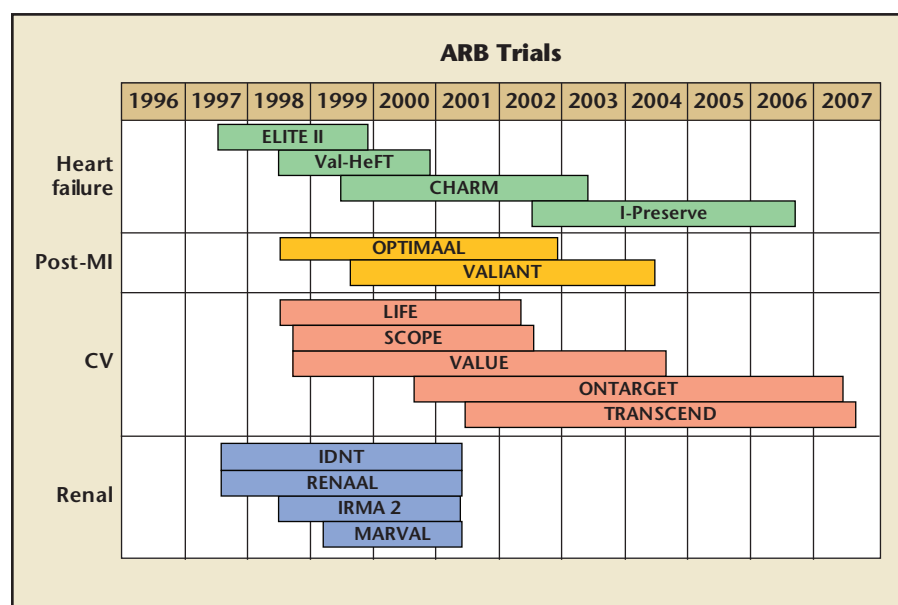
morning hours.[5-7] The precise mechanism underlying this increased risk is not known for certain. However, it is well known that there is a circadian pattern of blood pressure that, after a nighttime low, increases sharply in the morning before reaching a peak around noon. Associated with this increase in blood pressure in the early morning hours is an increase in blood viscosity, platelet adhesiveness, sympathetic nervous system activity, and activity of the renin-angiotensin-aldosterone system.
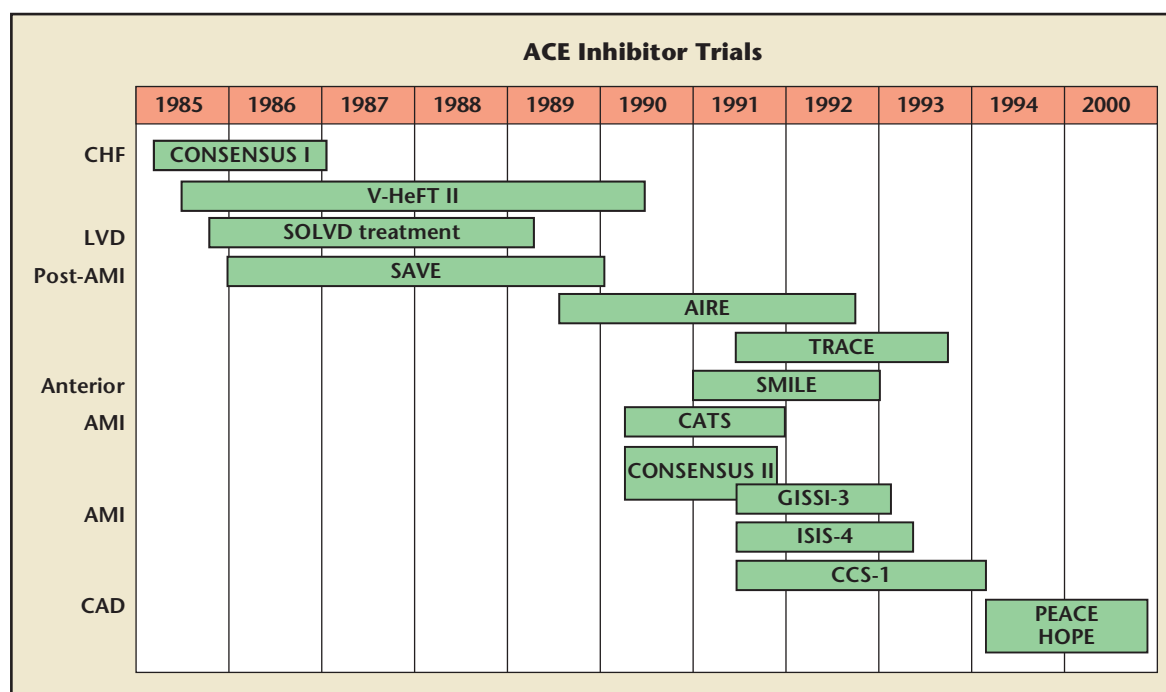
The blood pressure increase in the morning hours has led to the postulation that prevention of a sharp increase in blood pressure in hypertensive patients during the morning would result in a reduction in morbidity and mortality. A proper clinical trial design to evaluate this concept has not been executed to this date. Nevertheless, the logic appears clear.

The HOPE Trial—ACE Inhibitors in Increased Cardiovascular Risk

The first ACE inhibitor trial in subjects at high risk for cardiovascular morbidity and mortality was the Heart Outcomes Prevention Evaluation (HOPE) trial.[8] The HOPE trial enrolled 9297 subjects older than 55 years (age is the most important risk predictor) who had evidence of vascular disease or diabetes plus one other cardiovascular risk factor and who were not known to have a low ejection fraction or heart failure. Subjects were randomized to receive either ramipril (10 mg/d at bedtime) or placebo in addition to other drugs used to reduce blood pressure. Subjects with uncontrolled blood pressure were not allowed entry into the trial. After a mean of 5 years, subjects in the ramipril group experienced a reduction in the combined endpoint of myocardial infarction, stroke, or death from cardiovascular causes.

Figure 1. *The clinical trial development of the angiotensin receptor blockers (ARBs) since 1997. The last frontier is the role of ARBs in the treatment of high-risk patients with coronary disease, peripheral vascular disease, cerebrovascular disease, or diabetes with cardiovascular (CV) risk factors without evidence of heart failure or low ejection fraction. This use is the subject of the ONTARGET and TRANSCEND trials. ELITE II, Losartan Heart Failure Survival Study; Val-Heft, Valsartan Heart Failure Trial; CHARM, Candesartan in Heart Failure; I-PRESERVE, Irbesartan in Heart Failure with Preserved Systolic Function; OPTIMAAL, Effects of Losartan and Captopril on Mortality and Morbidity in High-Risk Patients After Acute Myocardial Infarction; VALIANT, Valsartan in Acute Myocardial Infarction Trial; LIFE, Losartan Intervention For Endpoint Reduction in Hypertension; SCOPE, Study on Cognition and Prognosis in Elderly; VALUE, Valsartan Antihypertensive Long-Term Use Evaluation; ONTARGET, ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial; TRANSCEND, Telmisartan Randomized AssessmeNt Study in ACE-I INtolerant Subjects with Cardiovascular Disease; IDNT, Irbesartan Diabetic Nephropathy Trial; RENAAL, Effects of Losartan on Renal and Cardiovascular Outcomes in Patients With Type 2 Diabetes and Nephropathy; IRMA 2, Irbesartan in Type 2 Diabetes With Microalbuminuria 2; MARVAL, Microalbuminuria Reduction with Valsartan.* ⬆ www.medreviews.com

ACE Inhibitor Trials

	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	2000
CHF	CONSENSUS I										
		V-HeFT II									
LVD		SOLVD treatment									
Post-AMI		SAVE									
						AIRE					
							TRACE				
Anterior						SMILE					
AMI					CATS						
					CONSENSUS II						
AMI						GISSI-3					
					ISIS-4						
					CCS-1						
CAD										PEACE HOPE	

Figure 2. *The time course of the clinical trials of angiotensin-converting enzyme (ACE) inhibitors in various cardiovascular disease states is shown. The trials culminated with the HOPE trial in subjects at increased cardiovascular risk. CONSENSUS, The Effects of Enalapril on Mortality in Severe Congestive Heart failure; V-HeFT, Vasodilator-Heart Failure Trial; SOLVD, The Effects of Enalapril on Survival in Patients with Reduced Left Ventricular Ejection Fractions and Congestive Heart failure; SAVE, Survival and Ventricular Enlargement Trial; AIRE, Acute Infarction Ramipril Efficacy Study; TRACE, The Trandolapril Cardiac Evaluation; SMILE, The Effects of the Angiotensin-Converting-Enzyme Inhibitor Zofenopril on Mortality and Morbidity after Anterior Myocardial Infarction; CATS, Captopril and Thrombolysis Study; GISSI, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico acuto; ISIS, International Study of Infarct Survival; CCS, Chinese Cardiac Study; PEACE, Prevention of Events With Angiotensin-Converting Enzyme Inhibition Trial; HOPE, Heart Outcomes Prevention Evaluation. Reprinted with permission from Latini R et al.[25]* www.medreviews.com

More recently, 2 trials of the ACE inhibitor perindopril—the European trial on Reduction of Cardiac Events with Perindopril (EUROPA) and the Prevention of Events with ACE Inhibition (PEACE) study—were also conducted in a high-risk population. In these studies, the event rates were lower than in the HOPE trial, and therefore the results were less dramatic.[9]

The ONTARGET and TRANSCEND Trials—ARBs in High Cardiovascular Risk

The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) and the Telmisartan Randomized AssessmeNt Study in ACE-I INtolerant Subjects

Table 1
JNC 7 CVD Risk Factors and Markers

Risk Factors	Markers
Age (> 55 years for men, > 65 years for women)	Estimated GFR < 60 mL/min
Hypertension*	Microalbuminuria
Cigarette smoking	
Obesity (BMI ≥ 30 kg/m^2)*	
Physical inactivity	
Dyslipidemia*	
Diabetes mellitus*	
Family history of premature CVD (men < 55 years or women < 65 years)	

*Components of the metabolic syndrome.
JNC, Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; CVD, cardiovascular disease; BMI, body mass index; GFR, glomerular filtration rate. Reprinted with permission from Chobanian AV et al.[3]

Table 2
The Pharmacokinetic Parameters of Various Angiotensin Receptor Blockers

	Telmisartan[18]	Losartan[19]	Irbesartan[20]	Candesartan[21]	Eprosartan[22]	Valsartan[23]	Olmesartan[24]
Usual dosage range	20 mg to 80 mg	25 mg to 100 mg	150 mg to 300 mg	8 mg to 32 mg	400 mg to 800 mg	80 mg to 320 mg	20 mg to 40 mg
Dosing frequency	qd	qd/bid	qd	qd	qd/bid	qd	qd
Terminal half-life (h)	~24	~2	11-15	9	5-9	6	13
Volume of distribution	500 L	34 L	53-93 L	0.13 L/kg	308 L	17 L	17 L
Renal elimination (%)	0.49 to 0.91	4	Unknown	26	7	13	35-50

with Cardiovascular Disease (TRANSCEND) study will attempt to answer the questions, "Are ARBs as useful as ACE inhibitors in reducing adverse outcomes in a high-risk population?" and "Does the combination of an ACE inhibitor and an ARB offer more protection than either one alone?"[10,11]

The trials will define high cardiovascular risk as a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes mellitus type 1 or 2 with end-organ damage (microalbuminuria, abnormal ankle/brachial index [< 0.8], or left ventricular hypertrophy). Patients with congestive heart failure will not be included. ONTARGET will investigate the efficacy of telmisartan monotherapy compared with ramipril monotherapy in preventing cardiovascular morbidity and mortality. The trial will identify any additional benefit of combining telmisartan with ramipril, compared with the ACE inhibitor alone. The TRANSCEND trial will consist of subjects who are intolerant to treatment with ACE inhibitors. It will determine if telmisartan is superior to placebo.

Recruitment has been completed, with 25,620 subjects randomized into ONTARGET and 5926 into TRANSCEND. The baseline patient characteristics are similar to those in the HOPE study, except for greater

ethnic diversity (including an important cohort from Asia). The subjects are slightly older. The mean blood pressure at randomization is again "normal," but slightly lower. Also, the use of beta-blockers and lipid-lowering therapy is higher in the trials than in the HOPE study. Primary endpoint data are expected in March 2008 for ONTARGET and October 2008 for TRANSCEND.

Pharmacological Characteristics of Telmisartan That May Predict Outcomes

Telmisartan is very effective at lowering blood pressure and has an excep-

tionally long duration of action (Table 2). Treatment with telmisartan and telmisartan/hydrochlorothiazide (HTCZ) resulted in significant reductions in mean 24-hour ambulatory blood pressure monitoring (ABPM), mean ABPM during the last 6 hours of the dosing period, mean ABPM during the first 4 hours of awakening, and mean office blood pressure.[6] Data from the Micardis Community Ambulatory Monitoring Trial (MICCAT-2), which utilized ABPM, also showed a prolonged effect of telmisartan.[12] It has been noted that this duration of action may be particularly effective in reducing the

Figure 3. *The comparative 24-hour effects of telmisartan (80 mg) and ramipril (10 mg) on systolic blood pressure (SBP) are shown. Telmisartan is more effective than ramipril throughout the 24-hour period, but particularly during the latter portion of the dosing cycle. Adapted with permission from Lacourcière Y et al.[26]* www.medreviews.com
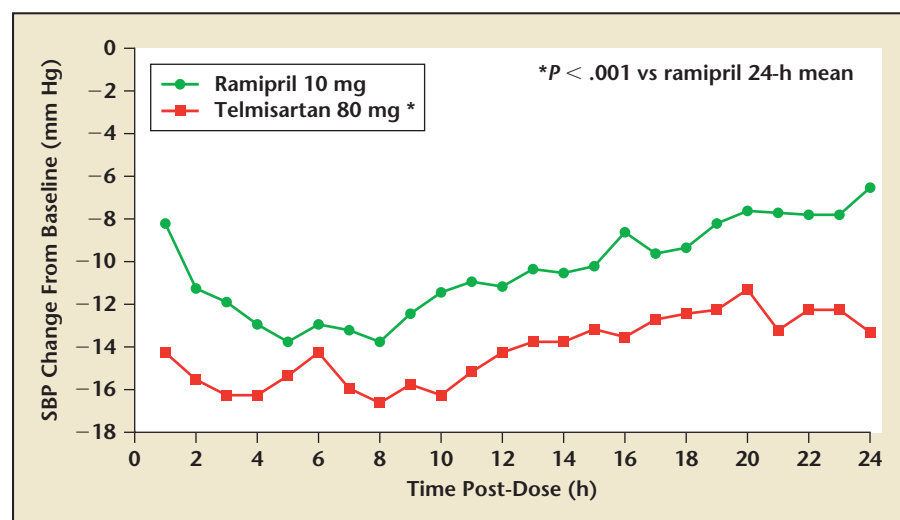
increased cardiovascular risk associated with the morning "surge" in systemic arterial blood pressure. It is possible that the ability of telmisartan to lower blood pressure for 24 hours could allow it to have a better outcome than ramipril (Figure 3).[13]

ARBs Plus ACE Inhibitors in the Management of Cardiovascular Disease

There is a great difference in the pharmacological characteristics of the ARBs and the ACE inhibitors. The preferred substrate for the ACE is bradykinin. In experimental studies in animals and humans, it has been demonstrated that the action of bradykinin is responsible for some of the ACE inhibitors' observed effects on systemic hemodynamics, as well as for some of their adverse events. ACE inhibitors reduce the generation of angiotensin II by inhibiting ACE; ARBs inhibit the binding of angiotensin II to the AT_1 receptor. ARBs reduce the generation of angiotensin II more effectively than ACE inhibitors because pathways other than the ACE (eg, chymase) exist for the conversion of angiotensin I to angiotensin II. The differences in pharmacology are shown in Table 3.

The combination of ACE inhibitors and ARBs in patients with heart failure has had some success in the Valsartan in Heart Failure Trial (ValHeft) and the Candesartan in Heart Failure (CHARM) trial.[14,15]

Will Effects on Blood Pressure Dominate?

Hypertension is not a disease associated with a specific threshold blood pressure.[16] Cardiovascular risk begins at a blood pressure level of approximately 115/75 mm Hg and doubles for each 20/10 mm Hg incremental increase. Thus, a 2 mm Hg reduction in blood pressure may be expected to result in a 7% reduction in ischemic heart disease mortality myocardial events and a 10% reduction in stroke mortality. At this point in time, it will be difficult to discern the mechanism of action of antihypertensive drugs apart from the simple reduction of blood pressure. It is now apparent that the degree to which blood pressure is lowered toward an optimal level primarily determines the effectiveness of antihypertensive treatment.[17]

The ONTARGET and TRANSCEND trials will provide valuable information regarding the use of telmisartan and ramipril in the treatment of subjects at high risk for cardiovascular morbidity and mortality with or without hypertension. The large amount of data and the careful way they are being gathered will permit new insights into treatment of high-risk populations. ∎

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Table 3
Pharmacological Differences in ACE Inhibitors and ARBs May Allow for Greater Beneficial Effects When Combined

	ACE Inhibition	AT_1 Blockade
Plasma renin and angiotensin I	↑	↑
Plasma angiotensin II	↓	↑
Stimulation of AT_1 receptors	↓*	↓
Stimulation of AT_2 receptors	↓	↑
Tissue bradykinin	↑	↔

*Incomplete at the tissue level.
ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; AT_1, angiotensin type 1; AT_2, angiotensin type 2.

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Main Points

• It has been recognized that dysregulation of the renin-angiotensin system may play a role in the pathophysiology of many cardiovascular and renal disease states, such as heart failure, left ventricular dysfunction, post-myocardial infarction, and proteinuric kidney disease.

• Researchers have postulated that prevention of the sharp increase in blood pressure in hypertensive patients during the morning would result in a reduction in morbidity and mortality.

• Treatment with telmisartan, a long-acting angiotensin receptor blocker, has resulted in significant reductions in mean 24-hour ambulatory blood pressure monitoring (ABPM), mean ABPM during the last 6 hours of the dosing period, mean ABPM during the first 4 hours of awakening, and mean office blood pressure.

• Two new trials, The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) and the Telmisartan Randomized AssessmeNt Study in ACE-I INtolerant Subjects with Cardiovascular Disease (TRANSCEND) study, will provide valuable information regarding the use of telmisartan and ramipril in the treatment of subjects at high risk for cardiovascular morbidity and mortality with or without hypertension.