"These findings are reassuring," Dr. Mauri said. "Although neither bare-metal stents nor drug-eluting stents were originally approved in the setting of acute myocardial infarction, it is probably the most important condition that we treat with stents. This study confirms that the same benefits that DES offer other patients in preventing restenosis exist for patients with MI, and there doesn't appear to be any trade-off in increased risk of repeat MI or death." She added that patients with a DES must be able to take prolonged dual antiplatelet therapy with aspirin and a thienopyridine for one year.

Because patients with MI are at higher risk for late stent thrombosis than patients with stable angina, longer follow-up is needed to monitor the outcome over time. Dr. Mauri said that she and her colleagues plan to continue follow-up and re-examine the findings when more data are available.

Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial

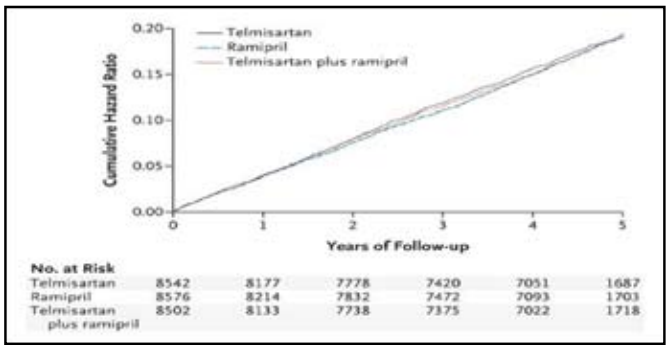
The angiotensin-receptor blocker (ARB) telmisartan is equally effective in reducing cardiovascular risk as the angiotensin-converting enzyme (ACE) inhibitor ramipril in patients with vascular disease or high-risk diabetes. However, the combination is no more effective than either drug alone and causes more side effects.

"Physicians and patients now have a choice as to whether to use telmisartan or ramipril," said Salim Yusuf, MD, McMaster University, Hamilton, Ontario, Canada, principal investigator of ONTARGET. "We can use telmisartan with confidence when we believe an ACE inhibitor is not tolerated," he said. Dr. Yusuf estimated that ACE intolerance affects "at least 20% to 30% of patients."

ONTARGET enrolled 25,620 patients with coronary heart disease or diabetes plus additional risk factors, but no evidence of heart failure. Patients were randomly assigned to treatment with ramipril 10 mg per day (n=8576), telmisartan 18 mg per day (n=8542), or the combination of ramipril and telmisartan (n=8502).

At a median follow-up of 56 months, a similar proportion of patients in each group reached the primary endpoint, a composite of death from cardiovascular causes, myocardial infarction (MI), stroke, or hospitalization for heart failure (Figure 1). Cardiovascular events were observed in 16.5% of patients in the ramipril group, compared with 16.7% in the telmisartan group (RR 1.01; 95% CI, 0.94-1.09) and 16.3% in the combination therapy group (RR 0.99; 95% CI, 0.92-1.07), suggesting that the three regimens were equally effective in preventing adverse cardiovascular outcomes.

Figure 1. Cardiovascular Events with Ramipril, Telmisartan, or Both.



Cough was the most common reason for discontinuation of therapy during ONTARGET (Table 1). Compared with the ramipril group, the telmisartan group had a lower rate of both cough (4.2% vs 1.1%; p<0.001) and angioedema (0.3% vs 0.1%; p=0.01). Patients in the telmisartan group were more likely than those in the ramipril group to report symptoms of hypotension (2.7% vs 1.7%; p<0.001), although both groups had a similar rate of syncope (0.2%). Patients in the combination group were much more likely than the ramipril group to discontinue therapy due to hypotensive symptoms (RR 2.75; p<0.001) and syncope (RR 1.95; p=0.03).

Table 1: Treatment Discontinuations with Ramipril, Telmisartan, or Both.

Variable	Ramipril (n=8576)	Telmisartan (n=(8542)	Combination Therapy (n=8502)	Telmisartan vs Ramipril		Combination Therapy vs Ramipril	
	number (percent)			RR	p Value	RR	p value
Total no. of discontinuations†	2099 (24.5)	1962 (23.0)	2495 (29.3)	0.94	0.02	1.20	<0.001
Reason for permanent discontinuation							
Hypotensive symptoms	149 (1.7)	229 (2.7)	406 (4.8)	1.54	<0.001	2.75	<0.001
Synocope	15 (0.2)	19 (0.2)	29 (0.3)	1.27	0.49	1.95	0.03
Cough	360 (4.2)	93 (1.1)	392 (4.6)	0.26	<0.001	1.10	0.19
Diarrhea	12 (0.1)	19 (0.2)	39 (0.5)	1.59	0.20	3.28	<0.001
Angioedema	25 (0.3)	10 (0.1)	18 (0.2)	0.4	0.01	0.73	0.30
Renal impairment	60 (0.7)	68 (0.8)	94 (1.1)	1.14	0.46	1.58	<0.001

†A patient could have multiple discontinuations, since patients were encouraged to restart study medications whenever possible after discontinuation.

Findings for the major secondary outcome, a composite of cardiovascular death, MI, or stroke (modeled after the primary outcome of the Heart Outcomes Prevention Evaluation (HOPE) trial), occurred in 14.1% of patients in

the ramipril group and 13.9% of patients in the telmisartan group (RR 0.99; 95% CI, 0.91-1.07). Combination therapy was not significantly different than ramipril alone (RR 0.99; 95% CI, 0.92-1.07) with respect to this major secondary composite endpoint.

Based on these findings, Dr. Yusuf said that ramipril and telmisartan can be "used interchangeably" in this patient population. However, evidence from ONTARGET suggests that caution should be used if these agents are combined, because side effects were increased, without clear benefit.

Results of ONTARGET were published simultaneously with the late breaking trials session in the *New England Journal of Medicine* [The ONTARGET Investigators. *N Engl J Med* 2008;15:1547-59].

Data Suggest Approach to Hypertension Management Should Change

New data challenge the current guidelines for management of hypertension, which recommend initiating treatment with a diuretic and suggest monotherapy as the starting point of treatment. The ACCOMPLISH trial showed that a single-pill combination of an angiotensin-converting enzyme (ACE) inhibitor and a calcium channel blocker led to excellent blood pressure control and significantly reduced the risk of cardiovascular events in high-risk patients.

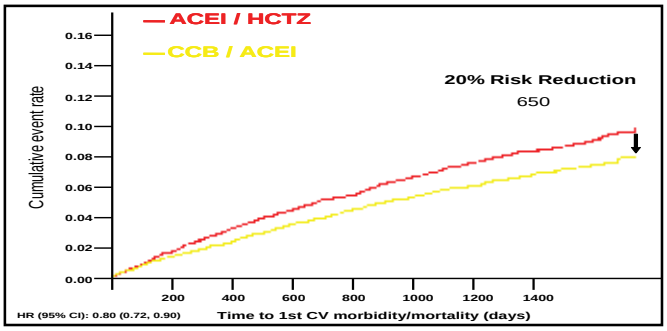
ACCOMPLISH was a multinational, double-blind clinical trial that enrolled patients at 550 centers in the US and Nordic countries. Patients were randomly assigned to treatment with a combination of an ACE inhibitor and a calcium channel blocker (benazepril/amlodipine) (5713 patients) or with a combination of the same ACE inhibitor and a thiazide diuretic (benazepril/hydrochlorothiazide) (5733 patients). The starting doses of amlodipine (5 mg), benazepril (20 mg), and hydrochlorothiazide (12.5 mg) were titrated to achieve a blood pressure <140/90 mm Hg or <130/80 mm Hg for patients with diabetes or renal insufficiency. Other antihypertensive agents (eg, beta blockers, alpha blockers, clonidine) could be added to achieve target blood pressure.

The mean age of the patients was approximately 68 years, and about 60% of patients were men. All patients had a systolic blood pressure of at least 160 mm Hg or were already being treated with antihypertensive agents. Before entry in the study, patients had received aggressive medical management, including frequent use of ACE inhibitors/angiotensin II receptor blockers (78%), lipid-lowering agents (67%), and oral antiplatelet therapies (63%).

The primary endpoint was cardiovascular morbidity and mortality, defined as cardiovascular-related death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, coronary revascularization procedure, or resuscitated sudden death. Kenneth Jamerson, MD, University of Michigan, Ann Arbor, MI, lead investigator of the study, noted that the trial was stopped early after an interim analysis by the Data Safety and Monitoring Committee demonstrated overwhelming efficacy (crossing of a prespecified efficacy boundary) in favor of benazepril/amlodipine.

Dr. Jamerson reported that at 30 months of follow-up, benazepril/amlodipine (CCB/ACEI) reduced the risk of cardiovascular morbidity and mortality by 20% compared with benazepril/hydrochlorothiazide (CCB/ACEI/HCTZ) (526 events vs 650 events; HR 0.80; 95% CI, 0.72-0.90; p=0.0002). In addition, the individual components of the primary endpoint also favored CCB/ACEI, with the exception of resuscitated sudden death (Figure 1). Blood pressure control improved significantly, from 37.5% to approximately 80% in both treatment groups (p<0.001), and approximately half of the patients in each group needed no antihypertension agents other than the study drugs.

Figure 1. Primary Endpoint.



In the intent-to-treat population in ACCOMPLISH, the composite primary endpoint and its individual components favored CCB/ACEI compared with ACEI/HCTZ. The exception was resuscitated sudden cardiac death. The data shown represent the incidence of adjudicated primary endpoints, based on a cutoff analysis date of March 24, 2008.

"The results of ACCOMPLISH provide compelling evidence for initial combination therapy with an ACE inhibitor and a calcium channel blocker, and these results challenge current diuretic-based guidelines," said Dr. Jamerson.