CARDIOLOGY Rounds®

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Vascular protection update 2008: the ONTARGET study

By BETH L. ABRAMSON, MD, FRCPC, FACC

The renin-angiotensin-aldosterone system (RAAS) is a hormonal system that regulates blood pressure (BP) and fluid balance; it constitutes an area of important research interest in the management of cardiovascular disease (CVD). This issue of *Cardiology Rounds* reviews the concept of vascular protection via renin-angiotensin system (RAS) blockade, as well as the clinical trial data to date supporting this concept. Further, the issue examines the results and clinical implications of the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) in patients at increased CV risk, fostering discussion regarding RAS blockade.

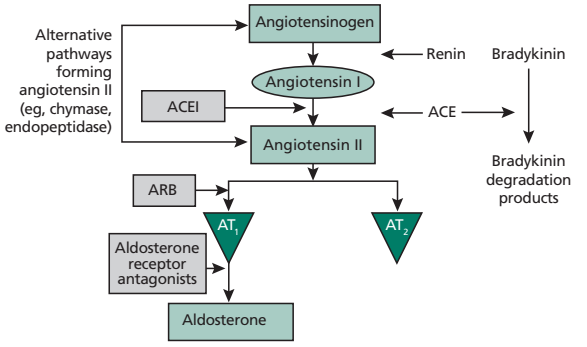
Angiotensin II, the primary mediator of the RAAS, plays a pivotal mechanistic role in the pathogenesis of hypertension. The RAAS involves a cascade of enzymatic reactions, whereby renin acts on angiotensinogen to produce angiotensin I. Angiotensin I is converted to angiotensin II by the action of the angiotensin-converting enzyme (ACE) that contributes to the breakdown of bradykinin into inactive peptides. ACE inhibitors (ACEIs) were the first class of agents to reveal activity in this neurohormonal system by interfering with the formation of angiotensin II; however, alternative pathways involving other enzymes, such as chymase or endopeptidase, also participate in angiotensin II synthesis. The actual clinical significance of these enzymes in angiotensin II formation remains to be clarified. Inhibition of ACE increases bradykinin levels that are thought to account for some benefits and side effects (such as angioedema and cough) of ACEIs (Figure 1). ACEIs reduce rates of death, myocardial infarction (MI), stroke, and heart failure (HF) among patients with previous vascular disease alone,[1,2] high-risk diabetes,[3] congestive heart failure (CHF),[4-6] or left-ventricular (LV) dysfunction.[7] In addition, vascular protective effects from ACEIs in coronary patients with preserved LV function have been documented.[8]

Angiotensin II receptor blockers (ARBs) constitute an alternative class of antihypertensive agents. ARBs are a specific therapeutic tool that antagonizes the RAAS through the selective blockade of the angiotensin II AT1 receptors, thereby inhibiting the effects of angiotensin II. Since ARBs bind directly to the AT1 receptors rather than inhibiting the formation of angiotensin II, they selectively interfere with the effects of this potent vasoconstrictor, regardless of the multiple pathways involved in its production.

In patients with HF, angiotensin II levels may increase and symptoms worsen, despite the use of ACE inhibitors. The use of an ARB in patients with a low ejection fraction and HF, who either could not tolerate an ACEI or were already receiving one, has been shown to reduce the rate of death or HF hospitalization.[9,10] ARBs have been studied in other populations as well. In hypertensive patients with LV hypertrophy, ARBs reduced vascular events in comparison with beta-blockers. Theoretically there should be fewer side effects, but similar efficacy in CV protection with an ARB rather than an ACEI; however, the reasons for benefits from these drugs in patients with preserved LV systolic function are complex and must be proven in clinical trials. In addition, data from small studies in patients with renal disease suggest that more complete blockade of the RAAS may be beneficial, either by using ACEIs and ARBs in combination, or in very high doses. Nevertheless, most trials to date have not examined the hard endpoint of mortality, and most have not taken cardiac patients into account; rather, they have focused on the important, but specific, population with severe renal dysfunction.

St. Michael's Hospital
30 Bond St.,
Suite 7049, Queen Wing
Toronto, Ont. M5B 1W8
Fax: (416) 864-5941

Figure 1: The renin-angiotensin-aldosterone system (RAAS)



ACEI: Angiotensin-converting enzyme inhibitor
ARB: Angiotensin II receptor blocker

Since patients experience side effects with ACEIs, it is important to recognize that an ARB could be used as an alternative for "vascular protection," ie, in those patients without LV dysfunction, or hypertension, in whom ACEIs have demonstrated benefits. Despite variable practice patterns to date, the role of ARBs as an alternative or an addition to ACEIs in preventing negative CV outcomes has not been clarified.

ONTARGET

The ONTARGET study[11] addressed the important clinical question about the role of ARBs, ie, do they have vascular protective effects in patients with preserved systolic function? In addition, the study was designed to determine whether a more complete blockade of the RAAS, with an ACEI and an ARB, in patients with normal systolic function was better than an ACEI alone. Specifically, the ONTARGET investigators evaluated whether the ARB, telmisartan, was not inferior to the ACEI, ramipril, and whether a combination of the 2 drugs was superior to ramipril alone in the prevention of vascular events in high-risk patients, who had CVD or diabetes mellitus (DM), but did not have heart failure.

The primary objectives of ONTARGET were to determine the effectiveness of 80 mg of telmisartan daily, as compared with 10 mg of ramipril daily. A "noninferiority" study, the clinical question as to whether telmisartan was "similar" to ramipril was tested, as well as the effectiveness of the combination compared with ramipril alone. The primary outcome was a "hard-endpoint" composite outcome of death from CV causes, MI, stroke, or hospitalization for heart failure. The main secondary outcome was a composite of death from CV causes, MI, or stroke, ie, the primary outcome in the Heart Outcomes Prevention Evaluation (HOPE) trial.[1] Other secondary outcomes were new HF, DM, atrial fibrillation, dementia or cognitive decline, nephropathy, and revascularization procedures. Other outcomes were death from any cause or from non-CV causes, angina, transient ischemic attack, development of LV hypertrophy, microvascular complications of diabetes, changes in blood pressure (BP) or in the ankle-brachial index, and new cancers.

Patient Population

The patient population was similar to the HOPE study, with the exception that diabetic patients were 'sicker," ie, target-organ damage was a criterion to enter the study (an enriched population). In contrast, in the HOPE study, patients with DM required risk factors, but not necessarily target-organ damage. Inclusion criteria were essentially selecting patients ≥55 years old with either: coronary artery disease, peripheral artery disease, cerebrovascular disease, or high-risk DM with evidence of end-organ damage. Patients were excluded if they had: an inability to discontinue either medication; a hypersensitivity or intolerance to ACEIs or ARBs; symptomatic HF, significant primary valvular or outflow tract obstruction, constrictive pericarditis, syncope of unknown etiology, revascularization (bypass or angioplasty) within 3 months, or uncontrolled hypertension; significant renal- artery stenosis or hepatic dysfunction; or other medical conditions or social reasons.

ONTARGET involved patients at 733 centres in 40 countries. The trial was coordinated and data were gathered and analyzed by the Population Health Research Institute at McMaster University and Hamilton Health Sciences, with coordinating suboffices at Oxford University and the University of Auckland under the sponsorship of Boehringer Ingelheim.

Run-in period and randomization

After informed consent, patients entered a single-blind, run-in period in which they received 2.5 mg of ramipril once daily for 3 days, followed by 40 mg of telmisartan and 2.5 mg of ramipril once daily for 7 days and then 5 mg of ramipril plus 40 mg of telmisartan for 11 to 18 days. Of the 29,019 patients who entered the run-in period, 3,399 (11.7%) were excluded from the study: 1,123 (3.9%) had poor compliance, 597 (2.1%) withdrew from the study, 492 (1.7%) had symptomatic hypotension, 223 (0.8%) had elevated potassium levels, 64 (0.2%) had elevated creatinine levels, 872 (3.0%) had other reasons for exclusion, and 27 (0.1%) died.

For the first 2 weeks after all 25,620 patient were randomized, 8,542 patients were assigned to receive 80 mg of telmisartan once daily, 8,576 were assigned to receive 5 mg of ramipril once daily, and 8,502 were assigned to receive a combination of the 2 drugs. After 2 weeks, the dose of ramipril was increased to 10 mg/day, allowing the comparison between ramipril (10 mg) vs telmisartan (80 mg) and ramipril (10 mg) vs ramipril (10 mg) + telmisartan (80 mg).

Statistical analysis

A "noninferiority trial" must be well powered, and this requirement was satisfied in the ONTARGET study. The number of patients was determined by the rate of death from CV causes, MI, stroke, or hospitalization for HF asso-

Table 1: Key baseline characteristics

	Ramipril	Telmisartan	Combination
n	8,576	8,542	8,502
Age	66.4	66.4	66.5
% females	27.2	26.3	26.5
% CAD	74.4	74.5	74.7
% Stroke/TIA	21.0	20.6	20.9
% Diabetes	36.7	38.0	37.9
BP (mm Hg)	141.8/82.1	141.7/82.1	141.9/82.1
% Statins	61.0	62.0	61.8
% Antiplatelets	80.5	81.1	81.1
% β-blockers	56.5	56.9	57.4

CAD = coronary artery disease; TIA = transient ischemic attack; BP = blood pressure

ciated with ramipril in the HOPE trial. The sample size of 7,800 patients per arm provided 89% power for the noninferiority analysis and 93% for the combination arm superiority hypothesis. A noninferiority determination requires a hazard ratio for telmisartan compared with ramipril that is below a predefined margin, with telmisartan retaining most of the ramipril effect, as compared with placebo. The margin was determined by the results of the HOPE trial; the 40th percentile (0.794) was chosen as a more robust reference to describe the effect of ramipril. The relative risk was translated into an excess risk for placebo as compared with ramipril of 1.26. Thus, a noninferiority margin of 1.13 ensured that telmisartan retained at least one-half of the ramipril effect, if the upper limit of the one-sided 97.5% confidence interval (CI) for the hazard ratio was less than this value. Both hypotheses were tested using a one-sided type I error of 0.025. As well, a sensitivity analysis was performed according to the protocol by censoring data from patients who took the study drugs for <50% of the study period.

Results

At the beginning of the study, patients were 66 years old on average, with a mean BP of 142/82 mm Hg (Table 1). At 6 weeks, the mean BP was reduced by 6.4/4.3 mm Hg in the ramipril group, by 7.4/5.0 mm Hg in the telmisartan group, and by 9.8/6.3 mm Hg in the combination-therapy group. Patients in the telmisartan group and the combination-therapy group continued to have slightly lower BP levels throughout the study period (average reductions, 0.9/0.6 mm Hg and 2.4/1.4 mm Hg, respectively) than patients in the ramipril group.

Compliance was excellent throughout the study, with 80% of patients on medications in each arm at study end. However, patients tolerated the telmisartan alone better than ramipril alone, with more patients permanently discontinuing ramipril during the study period (Table 2).

Primary outcomes and death: The primary outcome occurred in 1,412 patients (16.5%) in the ramipril group, in 1,423 patients (16.7%) in the telmisartan group, and in 1,386 patients (16.3%) in the combination-therapy group (Figure 2 and Table 3). The upper boundary of the CI (1.09) for the relative risk of the primary outcome in the telmisartan group as compared with the ramipril group was significantly lower than the predefined noninferiority boundary of 1.13 ($P = 0.004$). However, the lower boundary of the CI (0.94) indicates that telmisartan was not superior to ramipril. The secondary outcome — death from CV causes, MI, or stroke — occurred in 1,210 patients (14.1%) in the ramipril group and in 1,190 patients (13.9%) in the telmisartan group (relative risk, 0.99; 95% CI, 0.91 to 1.07; $P = 0.001$ for noninferiority). The results were consistent for all components of the primary outcome; in addition, combination therapy was not significantly better than ramipril alone (relative risk, 0.99; 95% CI, 0.92 to 1.07).

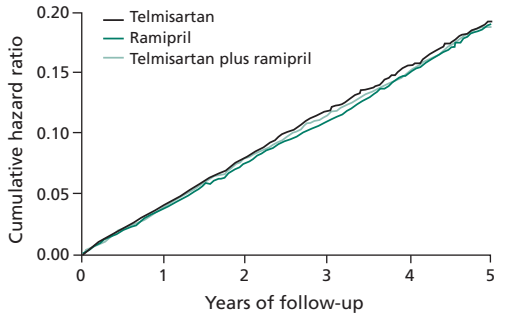
Adjustments for the small differences in BP did not materially alter the results for the primary outcome

Table 2: Reasons for permanently stopping study medications

	Ram n=8,576	Tel n=8,542	Ram vs. Tel RR	*P*
Hypotension	149	229	1.54	0.0001
Syncope	15	19	1.27	0.4850
Cough	360	93	0.26	<0.0001
Diarrhea	12	19	1.59	0.20
Angioedema	25	10	0.40	0.0115
Renal impairment	60	68	1.14	0.46
Any discontinuation	2,099	1,962	0.94	0.02

Ram = ramipril; Tel = telmisartan

Figure 2: Kaplan-Meier curves for the primary outcome in the 3 study groups



No. at risk						
Telmisartan	8542	8177	7778	7420	7051	1687
Ramipril	8576	8214	7832	7472	7093	1703
Telmisartan plus ramipril	8502	8133	7738	7375	7022	1718

The composite primary outcome was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure

Table 3: Incidence of the primary outcome, its components, and death from any cause

Outcome	Ramipril (n=8,576)	Telmisartan (n=8,542)	Combination therapy (n=8,502)	Telmisartan vs Ramipril	Combination therapy vs Ramipril
	number (percent			*risk ratio (95% CI)*	
Death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure*	1,412 (16.5)	1,423 (16.7)	1,386 (16.3)	1.01 (0.94–1.09)	0.99 (0.92–1.07)
Death from cardiovascular causes, myocardial infarction, or stroke†	1,210 (14.1)	1,190 (13.9)	1,200 (14.1)	0.99 (0.91–1.07)	1.00 (0.93–1.09)
Myocardial infarction‡	413 (4.8)	440 (5.2)	438 (5.2)	1.07 (0.94–1.22)	1.08 (0.94–1.23)
Stroke‡	405 (4.7)	369 (4.3)	373 (4.4)	0.91 (0.79–1.05)	0.93 (0.81–1.07)
Hospitalization for heart failure‡	354 (4.1)	394 (4.6)	332 (3.9)	1.12 (0.97–1.29)	0.95 (0.82–1.10)
Death from cardiovascular causes	603 (7.0)	598 (7.0)	620 (7.3)	1.00 (0.89–1.12)	1.04 (0.93–1.17)
Death from noncardiovascular causes	411 (4.8)	391 (4.6)	445 (5.2)	0.96 (0.83–1.10)	1.10 (0.96–1.26)
Death from any cause	1,014 (11.8)	989 (11.6)	1,065 (12.5)	0.98 (0.90–1.07)	1.07 (0.98–1.16)

* Patients could have multiple events in this category. The numbers of events were 2,058 (24.0%) in the ramipril group, 2,042 (23.9%) in the telmisartan group, and 2,000 (23.5%) in the combination-therapy group. The differences were not significant (P=0.83 for telmisartan vs ramipril, and P=0.38 for combination therapy vs ramipril).

† This composite was the primary outcome in the Heart Outcomes Prevention Evaluation (HOPE) trial.

‡ Patients could have multiple events in this category. The category includes both fatal and nonfatal events.

(relative risk for telmisartan vs ramipril, 1.02; 95% CI, 0.95 to 1.10; relative risk for combination therapy vs ramipril, 1.00; 95% CI, 0.93 to 1.07). There was no significant difference in the total number of deaths between the ramipril group and the telmisartan group (1,014 deaths and 989 deaths, respectively; relative risk in the telmisartan group, 0.98; 95% CI, 0.90 to 1.07); the number of deaths was higher in the combination-therapy group than in the ramipril group (1,065 deaths vs 1,014 deaths; relative risk in the combination-therapy group, 1.07; 95% CI, 0.98 to 1.16), but the difference was not significant.

Secondary outcomes: The rates of secondary outcomes revealed no significant differences (Table 4), except with renal dysfunction that occurred in 871 ramipril-group patients (10.2%), 906 patients (10.6%) in the telmisartan group, and 1,148 patients (13.5%) in the combination-therapy group. Table 5 presents the details of the renal outcomes.[12] As compared with the ramipril group, the telmisartan group had a similar relative risk of renal impairment (1.04), whereas the combination-therapy group had a significant increase in the relative risk (1.33, P<0.001). The rate of renal dialysis was the same in both ramipril and telmisartan

Table 4: Secondary and other outcomes

Outcome	Ramipril (n=8,576)	Telmisartan (n=8,542)	Combination therapy (n=8,502)	Telmisartan vs. Ramipril	Combination therapy vs. Ramipril
	number (percent			*risk ratio (95% CI)*	
Revascularization	1,269 (14.8)	1,290 (15.1)	1,303 (15.3)	1.03 (0.95–1.11)	1.04 (0.97–1.13)
Hospitalization for angina	925 (10.8)	954 (11.2)	952 (11.2)	1.04 (0.95–1.14)	1.04 (0.95–1.14)
Worsening or new angina	567 (6.6)	536 (6.3)	538 (6.3)	0.95 (0.84–1.07)	0.96 (0.85–1.08)
New diagnosis of diabetes*	366 (6.7)	399 (7.5)	323 (6.1)	1.12 (0.97–1.29)	0.91 (0.78–1.06)
Any heart failure	514 (6.0)	537 (6.3)	478 (5.6)	1.05 (0.93–1.19)	0.94 (0.83–1.07)
New atrial fibrillation†	570 (6.9)	550 (6.7)	537 (6.5)	0.97 (0.86–1.09)	0.96 (0.85–1.07)
Renal impairment‡	871 (10.2)	906 (10.6)	1,148 (13.5)	1.04 (0.96–1.14)	1.33 (1.22–1.44)§
Renal failure requiring dialysis	48 (0.6)	52 (0.6)	65 (0.8)	1.09 (0.74–1.61)	1.37 (0.94–1.98)

* The number of patients included in this analysis were 5,427 in the ramipril group, 5,294 in the telmisartan group, and 5,280 in the combination-therapy group.

† This category includes only patients who did not have atrial fibrillation at baseline: 8,296 in the ramipril group, 8,259 in the telmisartan group, and 8,218 in the combination-therapy group.

‡ No specific definitions were used. A determination of renal impairment was based on the clinical investigator's report of an event that led to the discontinuation of a study drug.

§ P<0.001.

Table 5: Renal outcomes[12]

	Ramipril n=8,576 %	Ramipril + Telmisartan n=8,502 %	Ram. + Tel. vs Ram. RR (95% CI)	*P* value
Any renal dysfunction*	10.04	13.35	1.33 (1.22-1.45)	<0.0001
Creatinine doubling	1.84	2.12	1.15 (0.93-1.42)	0.197
Potassium >5.5 mmol/L	3.32	5.67	1.71 (1.48-1.98)	<0.0001
Renal failure	0.28	0.64	2.27 (1.40-3.67)	0.0006
Need for dialysis	0.55	0.78	1.42 (0.98-2.06)	0.066
Death after renal dysfunction	1.84	2.21	1.20 (0.97-1.48)	0.087

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groups, with 48 patients (0.6%) and 52 patients (0.6%), respectively, undergoing dialysis, whereas the rate increased in the combination-therapy group, with 65 patients (0.8%) undergoing dialysis ($P = 0.10$ compared with the ramipril group).

Subgroup analyses: Comparisons of key subgroups demonstrated similar results between the ramipril group and the telmisartan group (Figure 3A) and between the ramipril group and the combination-therapy group (Figure 3B). These comparisons were also consistent in analyses adjusted for the use of various concomitant drugs (eg, statins, antiplatelet agents, beta-blockers, diuretics, and calcium-channel blockers) by patients.

Figure 3: Subgroup analysis

Figure 3A

Subgroup	No. of patients	Incidence of primary outcomes in Ramipril group (%)	Relative risk (95% CI)	*P*
Primary composite	17,110	16.5		
Cardiovascular disease				0.79
Yes	15,627	16.8		
No	1,405	13.1		
Systolic blood pressure				0.10
≤134 mm Hg	5,704	16.2		
135-150 mmg Hg	6,042	14.9		
>150 mm Hg	5,352	18.4		
Diabetes				0.97
Yes	6,381	20.7		
No	10,722	14.0		
HOPE risk score				0.21
≤3.677	5,751	10.1		
>3.677 to ≤4.050	5,620	15.0		
>4.050	5,747	24.4		
Age				0.65
<65 years	7,319	13.8		
65-74 years	7,310	17.3		
>75 years	2,407	24.2		
Sex				0.58
Male	12,537	16.7		
Female	4,581	15.8		

Figure 3B

Subgroup	No. of patients	Incidence of primary outcomes in Ramipril group (%)	Relative risk (95% CI)	*P*
Primary composite	17,070	16.5		
Cardiovascular disease				0.82
Yes	15,587	16.8		
No	1,404	13.1		
Systolic blood pressure				0.64
≤134 mm Hg	5,714	16.2		
135-150 mmg Hg	6,019	14.9		
>150 mm Hg	5,329	18.4		
Diabetes				0.15
Yes	6,355	20.7		
No	10,700	14.0		
HOPE risk score				0.97
≤3.677	5,676	10.1		
>3.677 to ≤4.050	5,570	15.0		
>4.050	5,032	24.4		
Age				0.75
<65 years	7,362	13.8		
65-74 years	7,177	17.3		
>75 years	2,539	24.2		
Sex				0.82
Male	12,497	16.7		
Female	4,581	15.8		

Discussion

This study indicates that telmisartan is clearly not inferior to ramipril for the primary outcome (death from CV causes, MI, stroke, or heart failure hospitalization), or for the important prespecified secondary (HOPE study) outcome (death from CV causes, MI, or stroke). Telmisartan exhibited slightly superior tolerability with less cough and angioedema, but increased mild hypotensive symptoms (no differences, however, in severe hypotensive symptoms, such as syncope). Higher rates of hypotension-related symptoms are consistent with the slightly lower BP levels associated with telmisartan, although the lower levels did not lead to further benefit.

Combination therapy did not reduce the primary outcome to any greater extent compared with ramipril alone and higher rates of adverse events were seen; therefore, there is no role for combination therapy as "vascular protection" in patients with normal LV function. One should not generalize these results to other populations in whom the RAS is more activated, such as HF patients in whom a more complete blockade of the RAS has demonstrated effectiveness. However, it does raise questions for the high-risk DM and CV patients with normal systolic function, since the harm observed was often renal. If combination ACEI and ARB medications are used for other reasons, it should be done with caution and with careful follow-up of electrolytes and kidney function.

To summarize, in the ONTARGET study, for CV patients with preserved LV function or high-risk diabetics, telmisartan was equally effective as an alternative to ramipril and is less likely to cause angioedema. This study should not be misinterpreted as dissuading a clinician from using ACEIs – they are proven to be beneficial – however, now clinicians have another option for therapy. The choice between the 2 agents will depend on the preferences of patients and physicians, as well as the individual susceptibility of a patient to specific adverse events. There is no additional advantage from the use of a combination of telmisartan and ramipril in full doses in this population, as compared with ramipril alone. The harm seen

in the combination arm of an ACEI and an ARB should raise questions on such practice until further data are available. This trial changes practice, in that it is the first in the preventive cardiology realm that offers the clinician another option for "vascular protection" treatment. It also raises many questions about more complete inhibition of the RAS with combination therapy, which it is hoped will be answered with further analysis of the data, and ongoing exploration of RAS blockade in various patient populations.

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Abstract of Interest

Elevations in serum creatinine with RAAS blockade: why isn't it a sign of kidney injury?

RYAN MJ, TUTTLE KR.

PURPOSE OF REVIEW: The aim of this article is to review the pertinent physiology and pathophysiology of the renin-angiotensin-aldosterone system (RAAS), summarize the proven beneficial cardiovascular and renal effects of RAAS blockade, examine clinical situations in which RAAS blockade may induce reductions in glomerular filtration rate, and explore why increases in serum creatinine in the setting of angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) therapy do not necessarily signify the presence of clinically relevant kidney failure.

RECENT FINDINGS: RAAS inhibition appears to reduce the likelihood of atrial fibrillation. RAAS inhibition leads to improved insulin sensitivity and glycemic control, but does not appear to prevent diabetes. The beneficial effects of ACEi/ARB therapy extend to those with significant renal disease. Combination ACEi/ARB is safe, and reduces proteinuria more than either agent alone in patients with macroalbuminuric nephropathy. Acute deteriorations in renal function that result from RAAS inhibition are usually reversible.

SUMMARY: RAAS blockade exerts potent hemodynamic, antihypertensive, and antiinflammatory effects, and slows progression of kidney disease beyond that due to lowering of blood pressure. The benefit extends to those with advanced disease. In spite of established benefit, ACEi and ARB therapy remains underutilized, in part due to concerns about acute deteriorations in renal function that result from interruption of the RAAS.

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