



Olmesartan Medoxomil for Hypertension: A Clinical Review

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ABSTRACT

Olmesartan medoxomil is the latest angiotensin II receptor blocker approved for use in the U.S. Potential advantages of this drug include once-daily dosing, an absence of significant adverse reactions, a well-tolerated side-effect profile, and a cost-effective average wholesale price. Olmesartan medoxomil is currently being used as an alternative therapeutic antihypertensive agent for patients intolerant of angiotensin-converting enzyme inhibitors. Future studies are needed to determine whether this agent might prove useful in the treatment of cardiovascular and renal disease as well.

OVERVIEW

In April 2002, the Food and Drug Administration (FDA) approved olmesartan medoxomil (Benicar®, Sankyo Pharma), for the treatment of hypertension. The latest in a growing class of agents known as the angiotensin II receptor blockers (ARBs), the drug works by inhibiting the

effects of angiotensin II, a potent vasoconstrictor and one of the key contributors to cardiovascular and renal disease.

Because of the detrimental effects associated with elevated levels of angiotensin II, retarding its actions has been a major focus in the treatment of chronic disease states such as hypertension, heart failure, and proteinuria. The angiotensin-converting enzyme (ACE) inhibitors remain the first-line therapy for these disease states; however, by virtue of their mechanism, olmesartan medoxomil and other ARBs appear to offer an effective and a better-tolerated alternative.

To date, the FDA has approved seven ARBs for use in the U.S. Of these, losartan (Cozaar®, Merck) was the first to be marketed, followed by valsartan (Diovan®, Novartis), irbesartan (Avapro®, Bristol-Myers Squibb), candesartan (Atacand®, AstraZeneca), telmisartan (Micardis®, Boehringer Ingelheim), eprosartan (Teveten®, Solvay), and, more recently, olmesartan medoxomil. Currently, all of the available ARBs have been approved only for the treatment of hypertension; however, this class of agents has also demonstrated effectiveness in preventing atheromas,¹⁻³ improving survival in patients with heart failure caused by systolic dysfunction,^{4,5} decreasing endothelial dysfunction,^{6,7} increasing fibrinolysis,⁸ reducing proteinuria, and preserving kidney function in diabetic patients.⁹ This article summarizes the pharmacology, pharmacodynamics, pharmacokinetics, adverse effects, and clinical efficacy of olmesartan medoxomil.

PHARMACOLOGY

Angiotensin II is the primary vasoactive hormone of the renin-angiotensin system and plays an important role in the pathophysiology of several chronic disease states. It is found in a variety of tissues and formed primarily from the conversion of

angiotensin I to angiotensin II, a reaction catalyzed by ACE. To a lesser degree, human chymase and other non-ACE pathways also generate angiotensin II.

Once synthesized, angiotensin II produces its biological effects by binding to either the angiotensin II-AT₁ or AT₂ receptor subtype. The AT₁ receptor is found in brain, renal, myocardial, vascular, and adrenal tissue. Angiotensin II-AT₂ receptors are located in the adrenal medullary tissue, uterus, and brain. AT₁ receptors mediate the majority of responses crucial to cardiovascular and renal function (Figure 1).

Less is known about the role of AT₂ receptors; however, when these receptors are stimulated, they can cause vasodilation and can decrease endothelium proliferation.¹⁰ Like all ARBs, olmesartan medoxomil exerts its pharmacological actions by selectively blocking angiotensin II-AT₁ receptor sites in the vascular smooth muscle, thus inhibiting the vasoconstrictor effects of angiotensin II.

Although the ARBs have some structural and pharmacokinetic differences, few pharmacological differences separate these agents from one another. One notable variation is the degree of binding to the AT₁ receptor compared with the AT₂ receptor; olmesartan medoxomil exhibits more than a 12,500-fold greater affinity for the AT₁ receptor than for the AT₂ receptor, making it theoretically the second most potent agent.

The order of binding affinity to the AT₁ receptor, compared with the AT₂ receptor, for the ARBs appears to be as follows:¹¹⁻¹³

valsartan > olmesartan medoxomil > candesartan > irbesartan > telmisartan > losartan > eprosartan

Because of a lack of head-to-head clinical trials, it is uncertain whether this order in-

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dicates differences in clinical efficacy.

One binding characteristic that is more likely to influence therapeutic efficacy is the ability of different agents in this class to bind competitively or noncompetitively to the AT₁ receptor. Levels of circulating angiotensin II can increase over time with a continuous blockade of angiotensin II receptors by the ARBs. The pharmacological effect of competitive antagonists (i.e., the active metabolite of eprosartan and losartan) can be overcome by elevated levels of angiotensin II, resulting in a shorter duration of action for these agents. As a result, twice-daily administration seems necessary for optimal 24-hour blood pressure (BP) control with eprosartan and losartan.

The therapeutic actions of noncompetitive antagonists (i.e., olmesartan, valsartan, irbesartan, telmisartan, and can-

desartan) are unaffected by increased amounts of angiotensin II, thus leading to longer terminal half-lives for these ARBs. With the noncompetitive antagonists, 24-hour BP control with once-daily dosing appears possible.¹⁴

PHARMACOKINETICS

Olmesartan medoxomil, which is administered as a prodrug, is rapidly and completely de-esterified to the active metabolite olmesartan (RNH-6270) during absorption from the gastrointestinal tract. Following the conversion of olmesartan medoxomil to olmesartan, virtually no further metabolism occurs. The bioavailability of olmesartan is approximately 26%, similar to that of losartan and valsartan.

Following oral administration, the peak plasma concentration (C_{max}) of olmesar-

tan is reached after one to two hours. The bioavailability of olmesartan is not affected by food.^{15,16} Olmesartan is eliminated in a biphasic manner, with a terminal elimination half-life of approximately 13 hours. It is highly bound to plasma proteins (99%) and does not penetrate red blood cells. Olmesartan takes approximately three to five days to reach a steady state, and there is no accumulation in plasma with once-daily dosing.

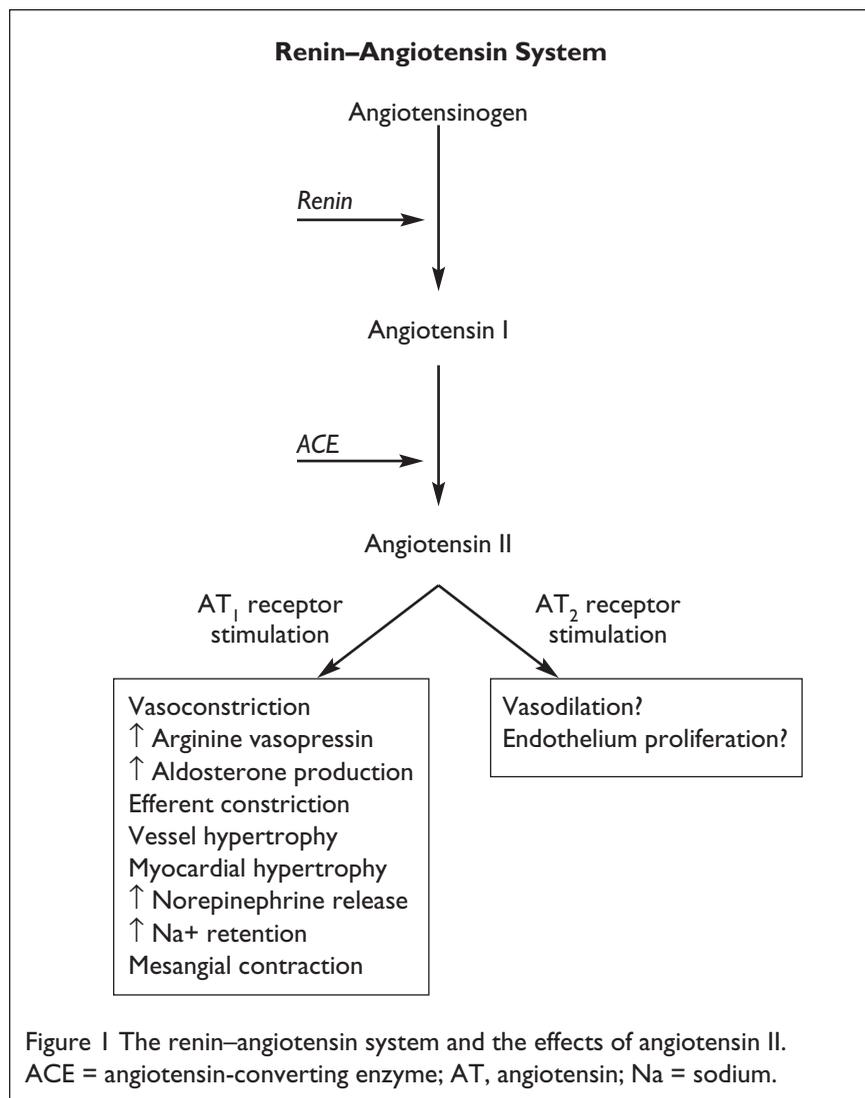
The pharmacokinetics of olmesartan medoxomil was studied in adults age 65 years and older. A modest accumulation was observed in these patients with repeated dosing; overall, however, maximum plasma concentrations were no different in the older patients than in those younger than 65. The pharmacokinetic profiles of the various ARBs are presented in Table 1.

ADVERSE EFFECTS

The safety and tolerability of olmesartan medoxomil have been evaluated in several clinical trials. Data were pooled from seven randomized trials involving a total of 3,095 patients with hypertension who received olmesartan medoxomil (2.5 to 80 mg/day) for six to 12 weeks.

Overall, patients tolerated the drug well, and the incidence of adverse events was similar to that for placebo (42.2% and 42.7%, respectively).¹⁷⁻²⁰ The most commonly reported side effects were headache, upper respiratory tract infections, and influenza-like symptoms. Dizziness was also frequently noted, with the incidence greater in these patients than in those receiving placebo (2.8% vs. 0.9%, *P* = .01). Six patients receiving olmesartan medoxomil discontinued therapy because of dizziness. The total discontinuation rates were 1.6% in the treatment group and 0.7% in the placebo group. Oparil et al.²¹ found that the rate of dizziness associated with olmesartan medoxomil (1.4%) was similar to the rates for losartan (0.7%), valsartan (1.4%), and irbesartan (3.4%).

Angioedema and a dry, persistent cough are two important class-related adverse events that may limit the use of ACE inhibitors. Levels of circulating ACE and, subsequently, substance P and bradykinin are unaffected by the ARBs, thereby reducing the potential for ACE inhibitor-induced cough or angioedema. In clinical trials, the incidence of cough was similar



for olmesartan medoxomil (0.9%) and placebo (0.7%).²² This rate is much lower than that reported in users of the ACE inhibitors; in those patients, cough has been noted to occur in up to 39% of cases.²³ Angioedema has rarely occurred with ARB therapy, although facial edema has been reported in five patients receiving olmesartan medoxomil.²²

During the first trimester of pregnancy, olmesartan medoxomil may be used with caution; it is considered a pregnancy category C drug during this time. Because of its potential to cause fetal and neonatal injury, however, it is considered a pregnancy category D drug during the last six months of therapy and should not be used unless the benefits outweigh the potential risks. Nonetheless, once a patient becomes pregnant, efforts should be made to discontinue therapy.²²

No studies evaluating the excretion of olmesartan in breast milk have been conducted; however, low concentrations of the drug have been detected in the milk of lactating rats. Therefore, it is possible that olmesartan might be excreted in human breast milk as well, and a decision to discontinue breast-feeding or the drug itself should be made.

DOSING

Olmesartan medoxomil is supplied as 5-, 20-, and 40-mg film-coated tablets. The usual recommended starting dose is 20 mg once daily (range, from 10 to 80 mg daily). Twice-daily dosing offers no advantage over the same total dose given once daily and is not recommended. After two weeks of therapy, the daily dose may be increased to 40 mg in patients needing further reduction of BP. Doses above 40

mg do not appear to have any greater effect. If BP is not controlled by olmesartan medoxomil alone, a diuretic may be added. Dosing adjustments do not appear necessary for elderly patients or for patients with moderate to marked renal dysfunction (creatinine clearance less than 40 ml/minute) or with hepatic dysfunction.²²

DRUG INTERACTIONS

Olmesartan medoxomil does not appear to have any clinically relevant drug interactions. The co-administration of antacids does not significantly alter its bioavailability,²⁴ and no clinically significant drug interactions have been reported with the co-administration of digoxin or warfarin.²⁵ Because olmesartan medoxomil is not metabolized by the cytochrome P-450 system, drugs that in-

Table 1 Pharmacokinetic Properties of the Angiotensin II Receptor Blockers

	Olmesartan²²	Losartan³⁰	Valsartan³¹	Irbesartan³²	Candesartan³³	Telmisartan³⁴	Eprosartan³⁵
Brand name	Benicar®	Cozaar®	Diovan®	Avapro®	Atacand®	Micardis®	Teveten®
Manufacturer	Sankyo Pharma	Merck	Novartis	Bristol-Myers Squibb	AstraZeneca	Boehringer Ingelheim	Solvay
F (%)	26	33	10–35	60–80	15	42–58	13
Active metabolite	Yes	Yes	No	No	Yes	No	No
T _{max} (hr)	1–3	1 (metabolite, 3–4)	2–4	1.5–2	3–4	No	1–2
t _{1/2} (hr)	12–18 (metabolite, 8–13)	2 (metabolite, 6–9)	6	11–15	3.5–4 (metabolite, 3–11)	Only 11% biotransformed	5–9
Metabolism (primary pathway)	De-esterification	CYP-2C9 and 3A4	Unknown	CYP 2C9	O-demethylation	Conjugation	Glucuronide conjugation
Elimination (%)	8–12 renal, biliary	35 renal, 60 biliary	10 renal, >80 biliary	20 renal, 80 biliary	33 renal, 67 biliary	>97 biliary	7 renal, 90 biliary
Food interactions	No	10% decrease in bioavailability	~50% decrease in AUC (NS)	No	No	6%–20% decrease in bioavailability	Delayed absorption (NS)
Drug interactions (significant)	None	Rifampin, fluconazole	None	None	None	Digoxin	None
Dose in hepatic impairment	No change in dose	↓ Initial dosage	No change in dose*	No change in dose*	No change in dose*	Use with caution	No change in dose
Dose in renal impairment†	No change in dose	No change in dose	No change in dose‡	No change in dose	No change in dose	No change in dose‡	No change in dose

* No change in dosage for mild to moderate hepatic dysfunction; exercise care in severe disease (no data available).

† No dosage adjustment necessary unless the patient is volume-depleted.

‡ No change in dosage for mild to moderate renal dysfunction; exercise care in severe disease (no data available).

AUC = area under the curve; CYP = cytochrome P-450; F = bioavailability; t_{1/2} = elimination half-life; T_{max} = time of maximum plasma concentration.

Table 2 Recommended Daily Dosage and Average Wholesale Price* of the Angiotensin II Receptor Blockers

	Olmesartan medoxomil	Losartan	Valsartan	Irbesartan	Candesartan	Telmisartan	Eprosartan
Brand name	Benicar®	Cozaar®	Diovan®	Avapro®	Atacand®	Micardis®	Teveten®
Manufacturer	Sankyo Pharma	Merck	Novartis	Bristol-Myers Squibb	AstraZeneca	Boehringer Ingelheim	Solvay
Approved indications	Hypertension	Hypertension and nephropathy in type 2 diabetic patients with hypertension	Hypertension and heart failure (NYHA classes II to IV)	Hypertension and nephropathy in type 2 diabetic patients with hypertension	Hypertension	Hypertension	Hypertension
Dosage form	5-, 20-, and 40-mg tablets	25-, 50-, and 100-mg tablets	80- and 160-mg capsules	75-, 150-, and 300-mg tablets	4-, 8-, 16-, and 32-mg tablets	20-, 40- and 80-mg tablets	400- and 800-mg tablets
Dosage range and frequency	5–80 mg daily	50–100 mg daily (may divide doses)	80–320 mg daily	75–300 mg daily	4–32 mg daily (may divide doses)	40–80 mg daily	400–800 mg daily (may divide doses)
AWP [†] / tablet or capsule	5 mg/\$1.31 20 mg/\$1.31 40 mg/\$1.31	25 mg/\$1.51 50 mg/\$1.51 100 mg/\$2.06	80 mg/\$1.47 160 mg/\$2.03	75 mg/\$1.50 150 mg/\$1.58 30 mg/\$1.90	4 mg/\$1.45 8 mg/\$1.45 16 mg/\$1.45 32 mg/\$1.96	20 mg \$.58 40 mg/\$1.58 80 mg/\$1.64	400 mg/\$1.03 600 mg/\$1.37

* The average wholesale price (AWP) is a published price list and does not represent the actual prescription-filling fee for the patient; this may be higher. The AWP cost (rounded to the nearest dollar) is based on the Red Book® Update. Montvale, NJ: Medical Economics Company, Inc.; 2002.
 NYHA = New York Heart Association.

duce, inhibit, or are metabolized by this enzyme do not appear to interact with it.

CLINICAL EFFICACY

Seven placebo-controlled studies involved 2,693 patients with essential hypertension; 2,145 patients received olmesartan medoxomil, and 548 patients received placebo. Doses ranged from 2.5 to 80 mg once daily for six to 12 weeks.

Patient responses to olmesartan medoxomil were dose-related; doses of 20 mg daily produced an overall reduction of sitting trough BP (the lowest measured BP with the patient sitting) of about -10/6 mm Hg over placebo, and doses of 40 mg daily produced an overall sitting trough BP reduction of about -12/7 mm Hg over placebo. Doses greater than 40 mg did not offer any additional effects.²⁰ Various published and unpublished comparative studies have also reported on the antihypertensive efficacy of olmesartan medoxomil.^{26–30}

Olmesartan Medoxomil versus Atenolol

The Van Mieghem Study

In a double-blind study,²⁶ 326 patients were randomly assigned to receive either

olmesartan medoxomil 10 mg once daily (n = 165) or atenolol 50 mg once daily (n = 161) for 12 weeks. If the desired response was not attained after four weeks of treatment, the dosage of either medication could be doubled.

After only two weeks of therapy, a decrease in the mean sitting diastolic BP at trough was seen in both treatment groups and became more pronounced during the next two weeks. The mean change from the baseline value in diastolic BP at 12 weeks was -14.0 ± 0.6 mm Hg for the olmesartan medoxomil group and -14.3 ± 0.6 mm Hg for the atenolol group. There was a small but significantly greater reduction in systolic BP from the baseline with olmesartan medoxomil (-20.7 ± 1.0) than with atenolol (-17.2 ± 1.0).

The Püchler Study

In another double-blind study,¹⁹ 328 patients with moderate to severe hypertension (mean sitting diastolic BP of 100 to 120 mm Hg receiving 25 mg of hydrochlorothiazide [HCTZ] daily) were randomly assigned to receive either olmesartan medoxomil (10 mg) once daily plus HCTZ or atenolol (50 mg) once daily plus HCTZ for 12 weeks. If the diastolic BP remained at or greater than 90 mm Hg

and/or had decreased by less than 10 mm Hg from the baseline after four weeks of therapy, the dosage of either drug could be doubled. Mean reductions in systolic BP and diastolic BP from the baseline were similar for the olmesartan medoxomil group (-20.4 ± 10.5/-17.3 ± 6.3 mm Hg) and the atenolol group (-19.6 ± 10.5/-17.2 ± 6.4 mm Hg).

Olmesartan Medoxomil versus Captopril

The Williams Study

In a multicenter, double-blind study,²⁷ 291 patients with mild to moderate hypertension (mean sitting diastolic BP of 95 to 114 mm Hg) were randomly assigned to receive either olmesartan medoxomil (5 mg) once daily or captopril (25 mg) twice daily for up to 12 weeks. The doses of either drug could be doubled after four weeks of therapy if the diastolic BP was at or above 90 mm Hg or had decreased less than 10 mm Hg from baseline values. The dosage of either drug could be doubled again after eight weeks if the diastolic BP remained uncontrolled.

The reduction in the seated trough diastolic BP from the baseline was greater in the olmesartan medoxomil group (-9.9 ±

0.6 mm Hg) than in the captopril group (-6.8 ± 0.6 mm Hg; mean difference -3.1 mm Hg, 95% confidence interval [CI] of $-4.8, -1.5$). In addition, reductions in mean systolic BP were greater in the olmesartan medoxomil group (-14.7 ± 1.1 mm Hg) than in the captopril group (-7.1 ± 1.1 mm Hg; mean difference -7.6 mm Hg, 95% CI of $-10.4, -4.7$).

Olmesartan Medoxomil versus Other Angiotensin II Receptor Blockers

The Ball Study

In a multicenter, double-blind study,²⁸ patients with mild to moderate hypertension (mean sitting diastolic BP of 95 to 114 mm Hg) were randomly assigned to receive either olmesartan medoxomil 10 mg once daily ($n = 158$) or losartan 50 mg once daily ($n = 152$) for 12 weeks. After four weeks of treatment, if the diastolic BP was greater than 90 mm Hg or had decreased less than 10 mm Hg from the baseline, the dose of either drug could be doubled. If the diastolic BP remained uncontrolled, HCTZ (12.5 mg) once daily could be added to the treatment regimen after 12 weeks and could be doubled after 16 weeks.

After 12 weeks, the mean reduction in seated trough diastolic BP in the olmesartan medoxomil group (-10.6 ± 0.5 mm Hg) was significantly greater than in the losartan group (-8.5 ± 0.6 mm Hg; mean difference -2.1 mm Hg, 95% CI of $-3.6, -0.5$). Further, the reduction in mean the seated systolic BP was greater in the olmesartan group than in the losartan group (-14.9 ± 1.0 vs. -11.6 ± 1.0 mm Hg; mean difference -3.3 mm Hg, 95% CI of $-6.0, -0.6$).

The Oparyl Study

In another multicenter, double-blind study,²⁹ 588 patients with hypertension (mean sitting diastolic BP of 100 to 115 mm Hg) were randomly assigned to receive one of four AII-receptor antagonists (olmesartan medoxomil 20 mg once daily, losartan 50 mg once daily, valsartan 80 mg once daily, or irbesartan 150 mg once daily) for eight weeks. After eight weeks, the mean reduction in the seated cuff diastolic BP from the baseline value was significantly greater in the patients receiving olmesartan medoxomil (-11 mm Hg) than in patients receiving losartan (-8.2 mm Hg, $P < .0002$), valsartan (-7.9 mm Hg;

$P < .0001$), or irbesartan (-9.9 mm Hg, $P = .0412$).

Although the reduction in the mean seated systolic BP was not significant, it was also greater in patients receiving olmesartan medoxomil than in those receiving losartan (-9.5 mm Hg), valsartan (-8.4 mm Hg), and irbesartan (-11.0 mm Hg). At week eight, the mean 24-hour ambulatory systolic BP was reduced significantly more with olmesartan medoxomil (-12.5 mm Hg) than with losartan and valsartan (-9.0 and -8.1 mm Hg; $P < .05$) but not more than with irbesartan (-11.3 mm Hg).

Conclusion

Results from these trials suggest that olmesartan medoxomil can be as effective as atenolol and more effective than captopril, losartan, valsartan, and irbesartan in reducing systolic or diastolic BP.

COST AND FORMULARY RECOMMENDATIONS

The average wholesale prices (AWPs) of olmesartan medoxomil and the other ARBs are listed in Table 2. The AWP does not directly reflect the price paid by the institution or group purchasing organization; at a cost of \$1.31/day, however, olmesartan medoxomil appears to be one of the more affordable agents in its class. Along with other potential advantages (i.e., once-daily dosing, no significant drug interactions, and a well-tolerated side-effect profile) olmesartan medoxomil is thus an antihypertensive agent worth considering as an addition to any formulary.

Ultimately, the decision to add olmesartan medoxomil to the formulary depends on whether (1) the AWP is reflective of the purchasing contract for institutions and (2) olmesartan medoxomil is granted FDA approval for the treatment of other disease states. In addition to the treatment of hypertension, some ARBs (losartan, valsartan, and irbesartan) have other FDA-approved indications, perhaps making them more attractive formulary products.

SUMMARY

Olmesartan medoxomil is the newest angiotensin II receptor blocker approved in the U.S. for the treatment of hypertension. It is well tolerated, with an adverse-effect profile similar to that of placebo,

except for the incidence of dizziness (which is greater with olmesartan medoxomil), and is devoid of any significant drug interactions. The drug provides smooth 24-hour BP control with once-daily dosing, and comparative studies suggest that it might have a greater efficacy than captopril, losartan, valsartan, and irbesartan.

Currently, olmesartan medoxomil has a place in therapy as an alternative antihypertensive agent for patients intolerant of ACE inhibitors. However, because the ACE inhibitors as well as some ARBs are also indicated for the treatment of heart failure, left ventricular dysfunction after myocardial infarction, and/or proteinuria, further studies are warranted to establish olmesartan medoxomil as a cardiovascular or renal protective agent.

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