Comparing Angiotensin II Receptor Blockers on Benefits Beyond Blood Pressure

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ABSTRACT

The renin-angiotensin-aldosterone system (RAAS) is one of the main regulators of blood pressure, renal hemodynamics, and volume homeostasis in normal physiology, and contributes to the development of renal and cardiovascular (CV) diseases. Therefore, pharmacologic blockade of RAAS constitutes an attractive strategy in preventing the progression of renal and CV diseases. This concept has been supported by clinical trials involving patients with hypertension, diabetic nephropathy, and heart failure, and those after myocardial infarction. The use of angiotensin II receptor blockers (ARBs) in clinical practice has increased over the last decade. Since their introduction in 1995, seven ARBs have been made available, with approved indications for hypertension and

some with additional indications beyond blood pressure reduction. Considering that ARBs share a similar mechanism of action and exhibit similar tolerability profiles, it is assumed that a class effect exists and that they can be used interchangeably. However, pharmacologic and dosing differences exist among the various ARBs, and these differences can potentially influence their individual effectiveness. Understanding these differences has important implications when choosing an ARB for any particular condition in an individual patient, such as heart failure, stroke, and CV risk reduction (prevention of myocardial infarction). A review of the literature for existing randomized controlled trials across various ARBs clearly indicates differences within this class of agents. Ongoing clinical trials are evaluating the role of ARBs in the prevention and reduction of CV rates of morbidity and mortality in high-risk patients.

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INTRODUCTION

Decisions surrounding antihypertensive treatment are influenced by the myriad of hypertension-induced (eg, heart failure [HF], ischemic heart or cerebrovascular disease, renal disease) and hypertension-associated (eg, type 2 diabetes [T2D] or prediabetes, atherosclerosis) conditions, with each additional cardiovascular (CV) risk factor potentiating the risk in a given patient.¹ Approximately 75% of the hypertensive population is estimated to have at least one additional CV risk factor (Figure 1).² With respect to HF, regarded as the most rapidly escalating CV condition in North America,³ up to 90% of cases are preceded by hypertension¹ and approximately one-third occur in conjunction with renal insufficiency.³ Overall, given that most patients with hypertension present with or develop comorbid CV and/or renovascular disease over their lifetime, blood pressure (BP) lowering is unlikely to be the sole goal of

treatment in these patients in whom broader risk factor reduction is necessary for influencing long-term morbidity/mortality.

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) lower BP through blockade of the renin-angiotensin-aldosterone system (RAAS), targeting the vasoconstrictive/antinatriuretic hormone angiotensin II.⁴ The RAAS has significance beyond hypertension given the putative role of angiotensin II in the pathogenesis of various CV (atherosclerosis, hypertensive left ventricular hypertrophy [LVH], HF- and atrial fibrillation [AF]-associated remodeling) and renal diseases.^{5,6} The adverse effect of angiotensin II on the CV system is multifaceted (Figure 2), with the promotion of oxidative stress representing only one of several mechanisms by which it may influence the pathogenesis of target organ damage.^{6,7} The ARB class was introduced into clinical practice in 1995, when losartan was granted approval as an antihypertensive, and

Figure 1. Coexistence of hypertension and cardiovascular/renal comorbidities (based on the National Health and Nutrition Examination Survey [NHANES] 2003-2004).² CAD=coronary artery disease; CHF=congestive heart failure; CKD=chronic kidney disease; Dys=dyslipidemia; MetS=cardiometabolic syndrome; PAD=peripheral arterial disease.

includes a total of seven agents approved for the treatment of hypertension (and, in some cases, for additional indications) (Table 1).^{8–14} A number of meta-analyses have calculated risk reductions for the ARB class of agents in areas outside of hypertension and, when taken together, suggest favorable effects in terms of preventing stroke and improving renal function and left ventricular (LV) mass, an uncertain risk/benefit profile in LV dysfunction and HF, and a potential increased risk for myocardial infarction (MI) in non-HF patients.^{15–22} Although conducting meta-analyses that capture multiple agents within a drug class is a common practice (with a tendency to also group data across ARBs and ACEIs to assess the broader RAAS inhibitor category) and may yield clinically interesting information, the results

and conclusions should not be interpreted as implying an overall class effect. In the case of the ARBs, important differences exist across the pharmacologic and pharmacokinetic profiles of the individual agents, including their binding affinity and selectivity for the angiotensin II type 1 receptor (AT₁).⁴ When given at their highest recommended doses for the treatment of hypertension, differences in BP lowering have been described.²³ Clinically, the extent to which the AT₁ binding affinity/selectivity-related differences within the ARB class influence BP control or long-term cardiorenal morbidity/mortality is unknown.⁴

The vast randomized controlled trial (RCT) experiences during which ARB-associated effects on outcomes beyond BP control have been compared with those for non-ARB agents are captured in Table 2.^{24–105} Herein, key RCTs of ARBs are reviewed with the intent to identify any notable distinctions among losartan, the first ARB introduced to treatment, and the other ARBs (valsartan, candesartan, irbesartan, telmisartan, eprosartan, or olmesartan) in terms of effectiveness outside of BP control. Relevant RCT data across the various agents will be discussed as well as additional RCTs, irrespective of size, that directly compared losartan against another ARB.

CLINICAL OUTCOMES BEYOND BP LOWERING IN RCT

Atherosclerosis

Key RCT Data for Losartan

Data for the antiatherosclerotic effects of losartan compared with another antihypertensive agent are only available from very small series, including a 57-patient Japanese study in which losartan led to no change in carotid intima-media thickness (IMT)

Figure 2. Schematic representation of the central role played by angiotensin (Ang) type 1 receptor-mediated signaling in hypertension and cardiovascular disease progression.⁵ AT₁R=angiotensin type 1 receptor; BP=blood pressure; MI=myocardial infarction; NE=norepinephrine.

Table 1. Approved indications and dosing for angiotensin II receptor blockers.

	Usual starting and maintenance dosing (as specified in the US product labeling)					
	Adult hypertension	Post-myocardial infarction	Heart failure (NYHA class II-IV)	CV risk reduction in ACEI-intolerance*	Stroke reduction in hypertensive LVH	Nephropathy in type 2 diabetes
Losartan ⁸	50 mg/day starting† 25-100 mg/day maintenance	Not indicated	Not indicated	Not indicated	50 mg/day starting‡ ↑ to 100 mg/day and/or add HCTZ§ per BP response	50 mg/day starting ↑ to 100 mg/day per BP response
Valsartan ⁹	80 or 160 mg/day starting† 80-320 mg/day maintenance	20 mg BID starting‡ ↑ to 40 mg BID within 7 days and titrate to target maintenance of 160 mg BID as tolerated**	40 mg BID starting ↑ to 80 mg BID and to target maintenance of 160 mg BID as tolerated	Not indicated	Not indicated	Not indicated
Candesartan ¹⁰	8 mg/day starting† 8 mg maintenance (usual) but may ↑ to 16 or 32 mg/day	Not indicated	4 mg/day starting ↑ to target maintenance of 32 mg/day as tolerated	Not indicated	Not indicated	Not indicated
Irbesartan ¹¹	150 mg/day starting† ↑ to 300 mg/day if needed	Not indicated	Not indicated	Not indicated	Not indicated	Target maintenance of 300 mg/day
Telmisartan ¹²	40 mg/day starting† 40-80 mg/day maintenance	Not indicated	Not indicated	80 mg/day starting 80 mg/day maintenance	Not indicated	Not indicated
Eprosartan ¹³	600 mg/day starting† 400-800 mg/day maintenance	Not indicated	Not indicated	Not indicated	Not indicated	Not indicated
Olmesartan ¹⁴	20 mg/day starting† ↑ to 40 mg/day if needed after 2 weeks	Not indicated	Not indicated	Not indicated	Not indicated	Not indicated

ACEI=angiotensin-converting enzyme inhibitor; BID=twice daily; BP=blood pressure; CV=cardiovascular; HCTZ=hydrochlorothiazide; LVH=left ventricular hypertrophy; NYHA=New York Heart Association.

*For reduction of myocardial infarction, stroke, or death from CV causes in patients age ≥55 years at high risk of major cardiovascular events and unable to tolerate ACEIs.

†If not volume depleted, in which case a lower starting dose should be used.

‡Evidence suggests that stroke reduction benefits do not apply to black patients.

§Initially 12.5 mg/day and then 25 mg/day subsequent to the losartan increase to 100 mg.

¶Specifically in clinically stable patients with LV failure or dysfunction, initiated as early as 12 hours post-myocardial infarction.

**Consider dose reduction for occurrence of symptomatic hypotension or renal dysfunction.

Table 2. Selected outcomes beyond blood-pressure lowering for which angiotensin II receptor blockers have been evaluated versus non-angiotensin II receptor blocker treatment in randomized controlled trials.

	Atherosclerosis	Hypertensive LVH	2° Prevention post-MI	Stroke	Heart failure	Atrial fibrillation	Renoprotection
Losartan	+/- ^{24,28}	+ (LIFE) ^{29,32}	- (OPTIMAAL) ³³	+ (LIFE*) ^{29,34} 2° prevent: + (LIFE) ³⁴	+/- (ELITE/ ELITE II) ^{35,37}	1° prevent: + (LIFE) ^{38,114}	+ (RENAAL, JLIGHT, ROAD) ³⁹⁻⁴¹
Valsartan	+ (MARVAL-2, VIP) ^{42,43}	+ ^{44,47}	+ (T-VENTURE, VALIANT) ^{46,49,50}	+ (Jikei Heart*, KYOTO HEART*) ^{51,52}	+ (Val-HeFT) ^{53,54}	1° prevent: + (Val-HeFT) ⁵⁶ 2° prevent: - (GISSI-AF) ⁵⁵ 2° prevent: - (CAPRAF) ⁷⁵	+ (VALERIA, SMART, HKVIN, MARVAL, MARVAL-2) ^{42,57-60}
Candesartan	+ (CENTRO, MITEC) ^{61,106}	+ (CATCH, CASE-I) ^{62,63}	- (E-COST) ⁶⁴	+ (SCOPE*) ^{65,66} 1° prevent: - (E-COST) ⁶⁴ 2° prevent: + (E-COST) ⁶⁴	+ (RESOLVD, CHARM) ^{67,74}	2° prevent: -	+/- (DIRECT, CENTRO) ^{61,76}
Irbesartan	+ (EPAS, ISLAND, SILVHIA) ⁷⁷⁻⁷⁹	+ (SILVHIA, CVIP) ⁸⁰⁻⁸²			+ (I-PRESERVE) ⁸³	2° prevent: + ^{84,85}	+/- (IRMA-2, IDNT, IMPROVE) ⁸⁶⁻⁸⁸
Telmisartan	+ ^{89,90}	+ (ONTARGET/ TRANSCEND) ⁹¹		- (TRANSCEND*) ⁹² 2° prevent: - (PROFESS) ⁹³	+ (REPLACE) ⁹⁴	1° prevent: + ⁹⁵	+/- (INNOVATION, TRANSCEND, ONTARGET, DETAIL) ⁹⁶⁻⁹⁹
Eprosartan	+ ¹⁰⁰	+ ¹⁰²		2° prevent: + (MOSES) ¹⁰⁴	+ (ADEPT) ¹⁰⁵		
Olmesartan	+ (EUTOPIA) ¹⁰¹	- ¹⁰³					

Note: + designates that the study achieved its primary or secondary endpoint(s); - designates that study did not meet its primary or secondary endpoint(s); this table is a summary of fully published randomized controlled trial data (ie, no data from single-arm noncomparative trials were considered), with an emphasis on large-scale trials (when available). Additional smaller studies were considered in the absence of data from large-scale clinical trials.

LVH=left ventricular hypertrophy; MI=myocardial infarction.

*Stroke data were not specific to primary or secondary prevention in the main analysis. †Stroke was evaluated in a post-hoc analysis, not as a prespecified endpoint.

among patients with hypertension (compared with a significant decrease with quinapril),²⁴ and a 13-patient Swedish study that showed significant improvement in endothelial function with losartan compared with atenolol in a hypertensive T2D population.²⁵ Improvements in arterial stiffness have likewise been reported for losartan in small hypertensive and hemodialysis populations, with effects similar to an ACEI in both settings and effects greater than atenolol for hypertension.^{26–28}

Key RCT Data for Other ARBs

In the AAA study (*for definitions of trial name abbreviations see the Appendix at the end of this document*), the reduction in IMT was significantly greater in amlodipine recipients than in ARB recipients, with a mean reduction of −0.046 mm compared with a mean increase of 0.080 mm in the ARB group ($P<0.05$).¹⁰⁶ The authors noted that the lack of ARB effect on IMT was an unexpected finding, and that the difference in IMT reduction was not attributable to a difference in BP reduction because there was no significant difference between amlodipine and ARB treatment in that regard.¹⁰⁶ Other

published RCT data pertaining to the potential antiatherosclerotic effects of the individual ARBs, including parameters related to endothelial function and arterial stiffness, are summarized in Table 3.^{42,61,77,101,107} Results of the MITEC study, in which 209 patients with T2D and mild-to-moderate essential hypertension were randomly assigned to receive candesartan 8–16 mg/day or amlodipine 5–10 mg/day (with addition of hydrochlorothiazide as needed), were recently published.¹⁰⁷ MITEC, specifically designed with the primary objective of determining the relative effects of candesartan and amlodipine on carotid artery IMT, was originally designed as a 3-year study but was closed early because of a high rate of early withdrawals (primarily for lack of BP control). Analysis of the data showed similar reductions from baseline to month 12, month 24, and last study visit in both treatment groups, with no statistically significant between-group differences at any time point. An encouraging finding was that more than 50% of patients per arm (56.5% and 59.0% of candesartan and amlodipine recipients, respectively; $P=0.82$) had carotid IMT regression from baseline to last study visit, supporting the theory that both

Table 3. Examples of antiatherosclerotic effects in selected randomized controlled trials* of angiotensin II receptor blockers.

Agent	Study	Key findings
Valsartan	MARVAL-2	Significant reduction in arterial stiffness with valsartan/HCTZ vs. amlodipine/HCTZ in hypertensive patients with albuminuria, which was independent of BP lowering ⁴²
Candesartan	CENTRO	Similar effects vs. enalapril on inflammatory markers of atherosclerosis in hypertensive patients with T2D ⁶¹
	MITEC	Similar effects vs. amlodipine on carotid IMT in hypertensive patients with T2D ¹⁰⁷
Irbesartan	SILVHIA	Greater effectiveness vs. atenolol in reducing common carotid IMT in hypertensive patients with LVH ⁷⁷
Olmesartan	EUTOPIA	Greater effectiveness vs. placebo in significantly reducing vascular microinflammation in a hypertensive population with a high prevalence of atherosclerotic disease ¹⁰¹

BP=blood pressure; HCTZ=hydrochlorothiazide; IMT=intima-media thickness; LVH=left ventricular hypertrophy; T2D=type 2 diabetes.

*In which the overall study population included >100 patients.

agents affect the natural progression of carotid IMT in hypertensive patients with T2D.

Comparative Trials of Losartan Versus Other ARBs

The AAA study was a Japanese open-label RCT that compared the impact of amlodipine (2.5–5 mg/day) and ARB treatment (losartan, telmisartan, valsartan, or candesartan) on the IMT of the carotid wall in 104 hypertensive patients with T2D.¹⁰⁶ Although losartan was a treatment option in the AAA study, only one patient received losartan. The results, as reported, provide no insight into the relative effects of the various ARBs because they only describe the ARB group as a whole.

Comment on the Antiatherosclerosis

Experience With Losartan Versus Other ARBs

Favorable antiatherosclerotic effects have been documented for losartan and for other ARBs in small RCTs. However, large-scale RCT data are lacking and, therefore, preclude any conclusions supporting or refuting the role of ARBs in improving atherosclerosis-related outcomes. The relative effect of losartan versus the effect of other ARBs on parameters, such as carotid IMT, is unknown.

Left Ventricular Remodeling in Hypertensive Patients

Key RCT Data for Losartan

Benefits of losartan with respect to LVH regression were evident in the results of the primary analysis and a series of subanalyses of the landmark LIFE study. In this study, more than 9000 patients with previously treated or untreated hypertension and electrocardiography (ECG)-documented LVH received losartan 50–100 mg/day or atenolol 50–100 mg/day. Hydrochlorothiazide was added as needed.²⁹

Publications derived from the LIFE study collectively support that losartan is significantly more effective than atenolol in not only reducing the composite of CV mortality/stroke/MI (primary endpoint), but also regressing LVH, as defined by the Cornell voltage-duration product and Sokolow-Lyon voltage criteria.^{29–32} After 1 year of treatment, patients with LV mass regression had significantly improved LV diastolic filling, an effect independent of BP lowering.¹⁰⁸ In another substudy, involving 754 LIFE participants with serial LV mass determinations at baseline and after 12 and 24 months, significant reductions in LV mass and relative wall thickness were seen during the second year of the study (despite only minor BP reductions beyond those achieved during the first year), supporting the theory that the benefits of sustained BP control continue to accrue over at least 2 years of treatment despite a plateau in BP reduction.¹⁰⁹

Key RCT Data for Other ARBs

Several other ARBs have been shown to improve hypertensive LVH relative to atenolol. In the SILVHIA study ($n=115$), similar BP reductions but significantly greater LV mass reductions were seen with irbesartan 150–300 mg/day compared with atenolol 50–100 mg/day ($\pm$ hydrochlorothiazide and felodipine as needed).^{80,81} These regimens were also compared in the CVIP study ($n=240$), which showed significant reductions in LVH voltage for irbesartan 150–300 mg/day compared with atenolol 50–100 mg/day (with hydrochlorothiazide and amlodipine as needed) after 6 and 18 months of treatment. LV mass reduction was not evident in the overall population but was seen after 18 months in patients with the highest baseline LV mass index values, with a numerically but not significantly greater reduction for irbesartan in this subgroup.⁸² Similarly, in a small RCT ($n=69$), treatment with

valsartan 80–160 mg/day ($\pm$ hydrochlorothiazide) for 8 months reduced LV mass index to a significantly greater extent than did atenolol 50–100 mg/day ($\pm$ hydrochlorothiazide).⁴⁶

There are other studies of ARB-induced effects on hypertensive LVH in which an agent other than atenolol was selected as the comparator regimen. For example, the effectiveness of candesartan in attenuating LVH in hypertensive populations was shown to be greater than that of amlodipine (in the CASE-J study [$n=4703$])⁶³ and similar to that of enalapril (in the CATCH study [$n=239$]).⁶² Each study supported similar BP-lowering effectiveness when the study regimens were compared. Most recently, LVH-focused results were published together for the ONTARGET ($n=25,620$) and TRANSCEND ($n=5926$) studies, both of which were international RCTs that enrolled patients at high risk for CV disease without HF or LV dysfunction and included ECG-determined LVH assessments.⁹¹ Telmisartan was associated with a significant 24% reduction in the adjusted odds of LVH ($P=0.0015$) during the 5-year follow-up of the placebo-controlled TRANSCEND, with a significant 35% reduction in new-onset LVH ($P=0.0001$) and a nonsignificant 9% odds of LV regression ($P=0.49$) for those with baseline LVH. Within the latter group, the LV regression subset had a significantly greater systolic BP reduction than the LV persistence subset (6.8 vs. 3.9 mmHg; $P<0.0001$). In ONTARGET, there was an 8% lower odds of LVH for telmisartan than ramipril that approached but did not reach significance ($P=0.07$).⁹¹ Comparisons of ARBs against amlodipine in small series in hypertension-associated LVH have produced variable findings. Whereas significantly greater LV mass reduction was seen with valsartan compared with amlodipine after 8 months in a Japanese study (along with significant reductions in monocyte-reactive oxygen

species and C-reactive protein),⁴⁷ no significant reduction was evident after 1 year of olmesartan or amlodipine in a more recently published US study.¹⁰³

Comparative Trials of Losartan Versus Another ARB

A small Italian RCT evaluated losartan (50–100 mg/day) and valsartan (80–160 mg/day) on LVH and LV function in 32 patients with mild to moderate untreated essential hypertension and associated concentric LVH, known to confer a particularly high risk for CV disease.¹¹⁰ Over 6 months, the regimens reduced systolic and diastolic BP to a similar degree. Significant reductions in LV mass index from baseline to the end of the 6-month study were observed with valsartan and with losartan; the effect for valsartan was significantly greater ($P<0.05$ vs. losartan). Significant improvements in predicted midwall fractional shortening and early peak/peak atrial velocity ratio occurred in both groups (no significant between-group differences), supporting the theory that the LV mass index reductions were associated with improvements in LV midwall systolic performance and in diastolic function in patients with concentric LVH.

Comment on the Hypertensive LVH Experience With Losartan Versus Other ARBs

The LIFE study of losartan showed favorable effects on hypertensive LVH. Encouraging data have been accumulating across various other ARBs. The results of one RCT of losartan compared with another ARB (valsartan) in hypertensive LVH have been published—a small study that showed a larger effect for valsartan on LV mass.¹¹⁰ However, it is insufficient for ascertaining clinically meaningful distinctions between these ARBs. Overall, with BP during treatment consistently noted to be similar

between groups in most of the comparative studies described here, the collective experience suggests that LVH improvements in ARB-treated patients with hypertension are independent of BP-lowering efficacy.

Secondary Prevention After MI

Key RCT Data for Losartan

Based on the OPTIMAAL study, losartan is not a suitable replacement for an ACEI after MI.³³ In this European study, nearly 5500 patients with confirmed acute MI and HF during the acute phase (or new Q-wave anterior infarction or reinfarction) were randomized to receive losartan (starting and target doses of 12.5 mg/day and 50 mg/day, respectively) or captopril (starting and target doses of 6.25 mg and 50 mg three times daily, respectively), with all-cause mortality as the primary endpoint. At the study end, mean doses being received were losartan 45 mg/day and captopril 44 mg three times daily. Regarding BP assessment, measurements were taken for 6 hours after the first dose and as part of the study follow-up, with significantly greater BP reduction seen during the first 2 hours with the starting dose of captopril 6.25 mg compared with losartan 12.5 mg. Specifically, at 1 hour post-first-dose, mean BP was 114/66 mmHg for captopril versus 119/69 mmHg for losartan ($P<0.0001$). The authors noted that BP was otherwise similar between the two groups. After a 2.7-year mean follow-up, the mortality rate was 18% in the losartan group and 16% in the captopril group, translating into a 13% greater risk for death with losartan that approached significance ($P=0.07$).

Key RCT Data for Other ARBs

Valsartan has been shown to affect post-MI LV function to the same degree as an ACEI,

supporting its approval for this indication. The VALIANT study, a three-arm comparison of valsartan (160 mg twice daily), captopril (50 mg three times daily), or valsartan (80 mg twice daily) plus captopril (50 mg three times daily) in nearly 15,000 patients with MI with complicating HF and/or LV dysfunction, showed no significant difference across the arms with respect to the primary endpoint of CV morbidity/mortality. ARB or ACEI monotherapy, however, was advantageous over combination treatment in terms of adverse events.⁴⁸ Per noninferiority analyses, valsartan was at least as effective as captopril in terms of preventing CV morbidity/mortality. A subset of the VALIANT participants were enrolled into the VALIANT Echo substudy ($n=610$), which found that the three study regimens also were similarly effective in improving ventricular structure and function over the 20-month post-MI period.⁴⁹

Recently published results of another RCT of valsartan compared with ACEI post-MI treatment, the T-VENTURE study, are consistent with those of VALIANT.⁵⁰ In this Japanese study that enrolled 256 patients with first acute MI, valsartan (dosed to a target of 160 mg/day) was as effective as an ACEI (one of seven agents) in protecting against LV dysfunction, as determined by left ventriculography repeated at 6 months after MI.⁵⁰ Another Japanese Study known as E-COST evaluated candesartan compared with other non-ARB/ACEI antihypertensive treatment on CV morbidity/mortality in 2048 patients with essential hypertension, showing a significant 57% reduction in MI ($P<0.05$). However, this finding was largely influenced by a 76% reduction among patients with no history of a CV event, with an insignificant 26% reduction among patients who experienced a previous MI or stroke.⁶⁴

Comment on the Secondary Prevention Post-MI Experience With Losartan Versus Other ARBs

Available RCT post-MI data for losartan, from a single trial, do not support benefits in this setting. Valsartan has been shown to be as effective as an ACEI in improving post-MI LV function and, therefore, has regulatory approval for this use. The relative post-MI effects of losartan compared with the other ARBs are unknown.

Stroke

Key RCT Data for Losartan

In the LIFE study, stroke was included as part of the primary composite endpoint, along with MI and CV mortality rate.²⁹ The ability of losartan to reduce the incidence of stroke by 25% (5% vs. 7% with atenolol; $P=0.001$) ranks among the most clinically notable findings of the LIFE study.²⁹ Stroke prevention was also evident in a subanalysis of the LIFE trial that focused on a subset of 6886 patients without known vascular disease.¹¹¹ As in the overall population, BP reductions were similar in this subset regardless of treatment with losartan or atenolol. However, with losartan there was a significant 19% reduction in the composite endpoint of CV death, stroke, and MI ($P=0.008$), which included an even greater 34% reduction in incident stroke ($P<0.001$).¹¹¹ Subanalysis by race showed that black individuals treated with losartan were actually at increased risk for stroke events than black individuals who received atenolol (unadjusted hazard ratio, 1.99), and this approached statistical significance ($P=0.051$).³⁴ Another LIFE subanalysis provided information for specific stroke subtypes, with a significant 35% reduction for losartan in terms of fatal stroke ($P=0.032$) and significant 27% reductions for the ischemic ($P=0.001$) and atherothrombotic

($P=0.002$) subtypes.³⁴ Incidences of embolic, hemorrhagic, and other/unclassified stroke were not significantly different between the two groups. The difference in recurrent stroke, however, was significant ($P=0.017$) with 26 losartan recipients compared with 46 atenolol recipients experiencing two or more incident strokes during the study follow-up.

Key RCT Data for Other ARBs

As in LIFE,^{29,34} most of the trials that evaluated stroke prevention for the other ARBs (Table 4) included incident stroke within the primary composite endpoint of CV morbidity/mortality, an exception being the PROfESS ($n=20,332$) secondary prevention study of telmisartan. Telmisartan had no impact on the primary endpoint of recurrent stroke after a 2.5-year mean follow-up in PROfESS⁹³ or on the composite component of stroke in the placebo-controlled TRANSCEND ($n=5926$).⁹²

Encouraging stroke prevention data have also been reported for valsartan,^{51,52} eprosartan (specifically as secondary prevention),¹⁰⁴ and candesartan.^{64,65} For example, in the Jikei Heart Study, valsartan 40–160 mg/day or a non-ARB was added to conventional treatment in 3081 Japanese patients with hypertension, coronary heart disease, and/or heart failure.⁵¹ The addition of valsartan lowered the incidence of stroke or transient ischemic attack by 40%, compared with non-ARB treatment ($P=0.028$). Similarly, in the KYOTO HEART Study ($n=3031$), the addition of valsartan 40–160 mg/day to existing treatment in Japanese patients with high-risk hypertension reduced the incidence of stroke or transient ischemic attack by 45%, compared with non-ARB treatment ($P=0.015$).⁵² In the placebo-controlled SCOPE trial, in nearly 5000 patients 70–89 years of age with mild to moderate hypertension, candesartan 8–16 mg/day was

Table 4. Examples of stroke-preventative effects in selected randomized controlled trials* of angiotensin II receptor blockers.

Agent	Study	Key findings
Losartan	LIFE	Overall stroke: significant stroke reduction vs. atenolol (25%; $P=0.0010$), ²⁹ with significant reductions in a subset without clinical vascular disease (34%; $P<0.001$) ¹¹¹ and in ischemic (27%; $P=0.001$), atherothrombotic (27%; $P=0.002$), and fatal (35%; $P=0.032$) stroke in a subanalysis of specific subtypes ³⁴ Secondary prevention: significant reduction ($n=26$ vs. $n=46$; $P=0.017$) in subtype-focused analysis ³⁴
	Jikei Heart Study	Overall stroke: significant reduction vs. non-ARB regimens (40%; $P=0.028$) in stroke or transient ischemic attack in patients with hypertension, coronary heart disease, and/or heart failure ⁵¹
Valsartan	KYOTO HEART Study	Overall stroke: significant reduction vs. non-ARB regimens (45%; $P=0.015$) in stroke or transient ischemic attack in patients with hypertension at high risk for cardiovascular events ⁵²
	SCOPE	Overall stroke: significant reduction vs. placebo (28%; $P=0.04$) in nonfatal stroke in elderly hypertensive patients, ⁶⁵ with significant all-stroke reduction in a subset with isolated systolic hypertension ⁶⁶
Candesartan	E-COST	Primary prevention: no significant stroke reduction vs. conventional antihypertensive treatment, with a 29% increased risk with candesartan in patients without history of stroke or MI ⁶⁴ Secondary prevention: significant stroke reduction for candesartan vs. conventional antihypertensive treatment in patients with past stroke or MI (61%; $P<0.01$) ⁶⁴
	PRoFESS	Secondary prevention: no significant recurrent stroke reduction (primary endpoint) vs. placebo when initiated within 90 days after ischemic stroke ⁹³
Telmisartan	TRANSCEND	Overall stroke: no significant stroke reduction vs. placebo in ACEI-intolerant patients with cardiovascular disease or diabetes/end-organ damage ⁹²
	MOSES	Secondary prevention: significant reduction vs. nitrendipine (25%; $P=0.026$) in fatal/nonfatal cerebrovascular events ¹⁰⁴
Eprosartan		

ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin II receptor blockers; MI=myocardial infarction.

*In which the overall study population included >100 patients.

associated with a significant 28% reduction in nonfatal stroke ($P=0.04$) and a 24% all-stroke reduction of borderline significance ($P=0.056$).⁶⁵ In a subanalysis of patients with isolated systolic hypertension, there was a significant 42% reduction in fatal/nonfatal stroke ($P=0.05$).⁶⁶ In the aforementioned E-COST evaluation of candesartan compared with other non-ARB/ACEI antihypertensive treatment in 2048 patients with essential

hypertension, there was a significant 39% reduction (5.8% vs. 9.4%; $P<0.05$) in stroke incidence for candesartan overall that was driven by the 61% reduction (18.3% vs. 46.9%; $P<0.01$) in patients with a CV history of stroke or MI.⁶⁴ From a primary prevention standpoint, however, the incidence of stroke was increased among those who received candesartan instead of the conventional treatment (3.5% vs. 1.2%; P value not reported).

Comment on Stroke Prevention Experience With Losartan Versus Other ARBs

Losartan lowered the risk for first stroke in the LIFE study, an effect that has since been documented for valsartan (in Jikei Heart and KYOTO HEART) and candesartan (in SCOPE but not in E-COST). In terms of secondary prevention, losartan appears to be effective (also per LIFE); however, the experiences with the other ARBs have been mixed. For losartan, stroke reduction in hypertensive patients with LVH is an approved indication. The relative effectiveness of losartan compared with other ARBs for primary or secondary stroke prevention is unknown.

Heart Failure

Key RCT Data for Losartan

The ELITE trial, a 48-week study in 722 elderly, ACEI-naïve patients with symptomatic HF, demonstrated a 9.4% rate of death and/or HF-related hospitalization for losartan (50 mg/day) compared with 13.2% for captopril (50 mg three times daily).³⁵ Although this 32% risk reduction was not significant ($P=0.075$), there was a significant difference in the all-cause mortality rate: 4.8% for losartan compared with 8.7% for captopril, a 46% reduced risk of death ($P=0.035$) that appeared to be largely influenced by a reduction in the occurrence of sudden cardiac death (1.4% vs. 3.8%). In the ELITE ventricular function substudy, in which 29 patients underwent radionuclide ventriculography at baseline and after 48 weeks, losartan and captopril prevented LV dilation to a similar degree, whereas only captopril induced reverse remodeling.³⁶ The intriguing survival benefit of losartan in ELITE prompted the design of a larger RCT of losartan compared with captopril to further assess mortality rate in a similar HF population (ELITE II [$n=3152$]). Unlike in

ELITE, however, the advantages for losartan in ELITE II pertained only to adverse event-related discontinuation rates, thereby suggesting that the between-group mortality rate differences in ELITE were likely the product of chance.³⁷ No differences between the two groups were apparent in the main ELITE II efficacy results (ie, all-cause mortality [primary endpoint], sudden death or resuscitated arrest, or all-cause mortality or hospitalization)³⁷ or in a subsequent report focused on HF-related outcomes (mortality, hospitalizations, discontinuations, change in New York Heart Association [NYHA] class, and quality of life [with significant improvements in the latter two parameters in both groups]).¹¹²

Key RCT Data for Other ARBs

Candesartan has shown favorable effects on ventricular function in patients with HF, initially in the RESOLVD study ($n=768$) in which the combination of candesartan and enalapril showed promise in preventing LV remodeling among patients with NYHA class II–IV congestive HF (CHF).⁶⁷

The CHARM program consisted of three concurrently conducted placebo-controlled RCTs in the following three symptomatic HF populations, based on LV ejection fraction (LVEF) and concurrent treatment: (1) patients with LVEF $>40\%$ (CHARM-Preserved); (2) LVEF $\leq 40\%$ receiving an ACEI (CHARM-Added); (3) and LVEF $\leq 40\%$ not receiving an ACEI owing to intolerance (CHARM-Alternative). A series of reports based on the overall CHARM program ($n=7599$), for which the primary outcome was all-cause mortality (23% candesartan vs. 25% placebo; $P=0.055$ [unadjusted] or $P=0.032$ [covariate adjusted]), support significant benefits for candesartan 32 mg/day in improving the rates of CV death and HF-related hospitalization,⁶⁸ sudden death and death from worsening HF,⁶⁹ and NYHA functional class.⁷⁰ In a combined

analysis of CHARM-Added and CHARM-Alternative, all-cause mortality, CV death, and HF hospitalizations were significantly lower for candesartan than for placebo in HF patients with LVEF $\leq 40\%$.⁷¹ Improvements in the primary outcome established for the individual trials (ie, CV death or unplanned hospitalization for management of worsening CHF) were achieved in CHARM-Added, including the subset of patients also receiving a beta-blocker,⁷² and CHARM-Alternative⁷³ but not in CHARM-Preserved.⁷⁴ (However, this third trial in patients with LVEF $>40\%$ showed fewer HF-related hospitalizations among candesartan recipients.)

The Val-HeFT study ($n=5010$) was designed to determine whether reductions in morbidity/mortality rate could be achieved by adding valsartan (target dose 160 mg twice daily) compared with placebo to an existing HF drug regimen (93% of patients were on ACEIs, 86% diuretics, 67% digoxin, and 35% beta-blockers), using coprimary endpoints of mortality alone or with morbidity (ie, cardiac arrest with resuscitation, HF-related hospitalization, or outpatient administration of intravenous inotropic or vasodilator drugs for ≥ 4 hours).⁵³ Mortality rate was nearly identical in the valsartan and placebo groups, at 19.7% and 19.4%, respectively. However, the combined mortality/morbidity outcome improved significantly among valsartan recipients to 28.8% compared with 32.1% with placebo, a significant 13% risk reduction ($P=0.009$). Within the mortality/morbidity composite, there was a notable difference in the rate of HF-related hospitalization: 13.8% compared with 18.2% with placebo. In the subset of patients who were not treated with an ACEI ($n=366$), regardless of beta-blocker use, valsartan treatment reduced the risk of morbidity/mortality by 44% and the risk of mortality by 33% compared with placebo.⁵³ However, in the subgroup receiving

valsartan, an ACEI, and a beta-blocker, mortality was significantly increased by approximately 40% ($P=0.009$) and there was a trend toward higher morbidity/mortality (nonsignificant 20% approximate increase; $P=0.10$). This finding suggested a potential negative effect of blocking multiple neurohormonal systems in patients with HF.

The reason for the difference between CHARM-Added and Val-HeFT with respect to the subset receiving triple therapy with an ARB, ACEI, and beta-blocker is not altogether clear. There are several differences between CHARM and Val-HeFT that could have influenced the results and may explain the differences between their outcomes. Compared to CHARM, Val-HeFT involved mainly NYHA class II patients and utilization of digoxin was higher while beta-blocker use was much lower (35%). CHARM involved more patients with NYHA class III disease, diabetes, and ischemic heart disease, and more patients receiving beta-blockers, spironolactone, and diuretics. The Val-HeFT echocardiographic study, which focused on measurements of LV internal diastolic diameter and LVEF, showed significant improvements in both parameters when valsartan was coadministered with an ACEI (without beta-blocker) or beta-blocker (without ACEI), but not when added to ACEI/beta-blocker combination treatment.⁵⁴ In patients who did not receive either an ACEI or a beta-blocker, treatment with valsartan significantly improved LV internal diastolic diameter and nonsignificantly improved LVEF. An additional analysis of the Val-HeFT echocardiographic data determined that the patients with the most severe LV remodeling derived the greatest benefit from valsartan.¹¹³

More recently, the placebo-controlled I-PRESERVE study ($n=4128$) failed to show improved outcomes for irbesartan 300 mg/day in patients with NYHA class II–IV HF with an

LVEF $\geq 45\%$.⁸³ Although RCT data are also available for eprosartan and telmisartan, they represent smaller, shorter-term studies that do not provide insight into the long-term benefits of these ARBs in patients with HF.^{94,105}

Comment on the HF Experience With Losartan Versus Other ARBs

Although ELITE suggested a role for losartan in patients with HF, no benefit was seen in the confirmatory ELITE II study, and results do not favor the use of losartan as a substitute to an ACEI. Recent data show that, in ACEI-intolerant patients, increased-dose losartan has a greater effect on reducing HF-related hospitalization than the conventional antihypertensive dose. The positive findings of RCTs of valsartan (Val-HeFT) and candesartan (CHARM) prompted their approval for use in patients with HF. The extent to which losartan reduces HF-related morbidity/mortality rates relative to the other ARBs is unknown.

Atrial Fibrillation

Key RCT Data for Losartan

Data from the LIFE study support that in patients with hypertension and ECG LVH, losartan offers additional advantages over atenolol in the primary prevention of AF.³⁸ Among losartan recipients, there was a 33% lower incidence of new-onset AF, a significant effect ($P<0.001$) that was independent of other known risk factors incorporated into the multivariate analysis.³⁸ A subsequent subanalysis found that the effects of losartan in reducing new-onset AF were associated with a reduction in LVH and independent of BP lowering.¹¹⁴ To better characterize the effects of RAAS blockade in the secondary prevention of AF, without the confounding influence of other comorbidities, Yin et al. randomly assigned

177 patients with lone paroxysmal AF to receive amiodarone alone, amiodarone plus losartan 50-100 mg/day, or amiodarone plus the ACEI perindopril 2-4 mg/day.¹¹⁵ In these groups, the incidences of recurrent AF within 24 months after randomization were 41%, 19%, and 24%, respectively, with significant advantages for both combinations compared with amiodarone in Kaplan-Meier analysis ($P=0.006$ for losartan/amiodarone; $P=0.04$ for perindopril/amiodarone) and a Cox proportional hazards model (in which the relative risks were 0.36 [$P=0.006$] and 0.39 [$P=0.008$], respectively). Significant reductions in left atrial diameter were also seen with both combinations relative to amiodarone monotherapy ($P<0.001$).

Key RCT Data for Other ARBs

AF-preventing effects have been reported for several other ARBs. In an RCT in 154 patients with a history of persistent AF assessed for recurrence during the 2 months after electrical cardioversion, irbesartan 150-300 mg/day plus amiodarone was associated with an 85% 2-month probability of maintaining sinus rhythm compared with 63% with amiodarone alone.⁸⁵ ARB use was identified as the only significant factor for maintaining sinus rhythm on multivariate analysis, translating into a 65% lower risk for recurrent AF than amiodarone alone ($P=0.018$) and an 81% reduction in a Cox proportional model that adjusted for factors such as diabetes, bundle-branch block, and AF duration ($P=0.031$). At last follow-up, after a median of 254 days, the probabilities of maintaining sinus rhythm were 80% and 56% for irbesartan/amiodarone and amiodarone, respectively. Valsartan subsequently was found to affect AF based on a post-hoc subanalysis of Val-HeFT that evaluated incident AF after add-on treatment with valsartan (target dose 160 mg twice daily) or placebo in patients

with class II-IV HF.⁵⁶ In 4395 patients with sinus rhythm at baseline, AF was reported as an adverse event in 5.1% of valsartan recipients compared with 8.0% of placebo recipients, translating into a highly significant 37% relative risk reduction on multivariate analysis ($P=0.0003$). The placebo-controlled GISSI-AF trial ($n=1422$) was subsequently designed specifically to evaluate the effects of add-on valsartan (target dose 320 mg/day) on the rate of recurrent AF.⁵⁵ Recently published results revealed no effect for valsartan on the primary outcome of first AF recurrence at 1 year (51% vs. 52% for placebo; adjusted hazard ratio 0.97; $P=0.73$) or the rate of multiple AF recurrences (27% vs. 28% for placebo; adjusted odds ratio 0.89; $P=0.34$). The results of GISSI-AF were consistent with those previously reported for the smaller CAPRAF study ($n=171$), in which postconversion candesartan 16 mg/day was no more effective than placebo in reducing the 6-month rate of recurrent AF among patients not receiving antiarrhythmic treatment.⁷⁵

Comment on the AF Prevention Experience With Losartan Versus Other ARBs

Data for losartan as AF prevention are limited, yet more favorable overall than those for the other ARBs, considering that negative results have been reported for several ARBs when evaluated specifically in patients with AF. Combining losartan or irbesartan with amiodarone appears to warrant further study in the prevention of recurrent AF. The relative effects of losartan compared with other ARBs as primary or secondary AF prevention are unknown.

Renoprotection

Data from RCTs detailing the renoprotective effects of ARBs are summarized in Table 5.^{39-42,57-61,76,86-88,96-99,116,117}

Key RCT Data for Losartan

Preventing nephropathy in patients with T2D is one of the approved indications for losartan. The results of the RENAAL study, published in 2001, clearly showed renoprotective benefits for losartan in patients with T2D and nephropathy (Table 5).³⁹ In RENAAL, 1513 patients received losartan 50-100 mg/day or placebo, in conjunction with conventional antihypertensive treatment, and were followed up for a mean of 3.4 years. The losartan group had a 16% risk reduction ($P=0.02$) for the primary composite endpoint of doubling of baseline serum creatinine (SCr), end-stage renal disease (ESRD), or death. The risk reductions for the individual renal outcomes within the composite were also significant (25% for SCr doubling [$P=0.006$] and 28% for ESRD [$P=0.002$]), whereas mortality rate was similar regardless of whether patients received losartan or placebo. The authors noted that differences in trough BP (albeit slightly lower among the losartan recipients) did not explain the renoprotective effects that were observed in RENAAL, with minimal change in the primary composite endpoint after adjusting for BP.³⁹ A number of smaller studies collectively suggest that the renoprotective effects of losartan treatment extend to populations beyond T2D nephropathy and are not attributable to the antihypertensive effects of losartan (Table 5).^{40,41}

The ROAD study ($n=360$) of ARB or ACEI monotherapy was unique in that it evaluated doses of losartan and benazepril in patients with nondiabetic proteinuria and chronic renal insufficiency titrated based on urinary protein excretion, SCr, and potassium levels, with a median of 100 mg/day for losartan (range 50-200 mg/day) and 20 mg/day for benazepril (range 10-40 mg/day).⁴¹ By tailoring treatment according to optimal antiproteinuric

Table 5. Examples of renoprotective effects in selected randomized controlled trials* of angiotensin II receptor blockers.

Type 2 diabetes			Other populations	
Agent	Study	Key findings	Study	Key findings
Losartan	RENAAL	Significant reductions in SCr doubling and ESRD in mostly hypertensive pts with T2D and nephropathy ³⁹	ROAD	Significant reductions in SCr doubling and ESRD when dosing losartan based on antiproteinuric effects in nondiabetic proteinuric chronic renal disease, with reductions similar to those with antiproteinuric benazepril dosing ⁴¹
	AMADEO	Significantly less effective in reducing proteinuria vs. telmisartan in hypertensive pts with T2D and nephropathy ¹¹⁶	JLIGHT	Significant reduction in proteinuria vs. amlodipine in pts with proteinuric chronic renal disease and hypertension (diabetic nephropathy allowed but population was mainly chronic glomerulonephritis) ⁴⁰
Valsartan	MARVAL	Significant reduction in microalbuminuria vs. amlodipine in normotensive or hypertensive pts with T2D and microalbuminuria ⁵⁷	MARVAL-2	Significant reduction in albuminuria with valsartan/HCTZ vs. amlodipine/HCTZ in hypertensive pts with albuminuria ⁴²
	SMART	Significant reduction in microalbuminuria vs. amlodipine in Japanese hypertensive pts with T2D and microalbuminuria ⁵⁸	VALERIA	Significant reduction in albuminuria and increase in rate of microalbuminuria normalization for valsartan/lisinopril vs. lisinopril alone in hypertensive pts with microalbuminuria ⁵⁹
	VIVALDI	Similar antiproteinuric effect vs. telmisartan in hypertensive pts with T2D and nephropathy ¹¹⁷	HKVIN	Significant reduction in proteinuria and slowing of GFR reduction vs. placebo in pts with IgA nephropathy ⁶⁰
Candesartan	CENTRO	Significant reduction in albuminuria vs. enalapril in hypertensive pts with T2D ⁶¹		
	DIRECT (3 studies)	No prevention of microalbuminuria vs. placebo in mostly normotensive pts with T1D or T2D ⁷⁶		
Irbesartan	IDNT	Significant reductions in SCr doubling and ESRD vs. amlodipine and placebo in hypertensive pts with T2D and microalbuminuria ⁸⁶	IMPROVE	No significant reduction in microalbuminuria for irbesartan/ramipril vs. placebo/ramipril in hypertensive pts with microalbuminuria and increased CV risk ⁸⁸
	IRMA-2	Significant reduction in nephropathy vs. placebo in hypertensive pts with T2D and microalbuminuria ⁸⁷		
Telmisartan	DETAIL	Similar renoprotection vs. enalapril in hypertensive pts with T2D and early nephropathy ⁸⁹	ONTARGET	Similar reduction in dialysis or SCr doubling and similar effects on albuminuria vs. ramipril in pts at high vascular risk, with a detrimental effect of combination treatment on dialysis/SCr doubling and in the primary composite (which included death) ⁹⁸
	VIVALDI	Similar antiproteinuric effect vs. valsartan in hypertensive pts with T2D and nephropathy ¹¹⁷	TRANSCEND	No significant improvement in composite of dialysis or SCr doubling vs. placebo in ACEI-intolerant pts with high vascular risk (CV disease or diabetes with EOD) but no macroalbuminuria, with a significant reduction in albuminuria but significantly greater GFR reduction with telmisartan ⁹⁷
	INNOVATION	Significant reduction in conversion from incipient to overt nephropathy vs. placebo in normotensive or hypertensive pts with T2D ⁹⁶		
	AMADEO	Significant reduction in proteinuria vs. losartan in hypertensive pts with T2D and nephropathy ¹¹⁶		

*In which the overall study population included > 100 patients.

ACEI=angiotensin-converting enzyme inhibitor; CV=cardiovascular; EOD=end-organ damage; ESRD=end-stage renal disease; GFR=glomerular filtration rate; HCTZ=hydrochlorothiazide; IgA=immunoglobulin A; pts=patients; SCr=serum creatinine; T1D=type 1 diabetes; T2D=type 2 diabetes.

effectiveness, losartan and benazepril significantly reduced the occurrence of SCr doubling, ESRD, or death by 53% ($P=0.022$) and 51% ($P=0.028$), respectively. There were no efficacy-related differences between losartan and benazepril at the conventional or antiproteinuric doses, and no dose-related increases in BP reduction or in adverse events.

Key RCT Data for Other ARBs

Much data support the theory that irbesartan (the only ARB other than losartan approved for preventing nephropathy in T2D) and several other ARBs (ie, valsartan, candesartan, and telmisartan) are renoprotective in patients with T2D (Table 5),^{57,58,61,86,87,96,99,116,117} more so than amlodipine and similar to ACEIs based on active-controlled evaluations.^{57,58,86,99} At the recommended target dose of 300 mg/day, irbesartan reduced the risk for SCr doubling/ESRD/death by 20% compared with placebo ($P=0.02$) and 23% compared with amlodipine ($P=0.006$) in the IDNT study ($n=1715$)^{86,87} and the onset of diabetic nephropathy by 70% compared with placebo ($P<0.001$) in the IRMA-2 study ($n=590$).⁸⁷ The IDNT and IRMA-2 studies both were conducted in hypertensive patients with T2D and determined that the renoprotection afforded by irbesartan was independent of BP lowering.^{86,87}

Reported RCT comparisons involving the other ARBs have shown renoprotective effects in T2D populations (Table 5). In the MARVAL study ($n=332$), for example, mean urinary albumin excretion rate improved by 44% at 24 weeks in patients treated with valsartan 80–160 mg/day, compared with only 8% in patients who received amlodipine 5–10 mg/day ($P<0.001$).⁵⁷ An exception to the favorable results obtained with most ARBs was reported in a pooled analysis of the three placebo-controlled studies within the DIRECT program.⁷⁶ Although the overarching

objective of the DIRECT program was to evaluate the effect of candesartan 32 mg/day on retinopathy in patients with diabetes (type 1 or 2), microalbuminuria was designated as a primary endpoint for the pooled analysis. After a 4.7-year median follow-up in the pooled analysis ($n=5231$), there was a nonsignificant 5% reduction ($P=0.60$) in incident microalbuminuria among candesartan recipients compared with placebo recipients. The authors proposed that the lack of renoprotection may have been influenced in part by the dominance of normotensive patients (with a corresponding low vascular risk) in this series of studies.⁷⁶ In this regard, although the majority of data support that ARB-induced renoprotection is not a BP-related phenomenon, there are reports in which improved renal outcomes have been associated with improved BP control.¹¹⁷

Overall, RCTs of valsartan, irbesartan, and telmisartan in nondiabetic renal disease have yielded mixed findings. The 133-patient VALERIA study found that the combination of valsartan 320 mg/day plus lisinopril 20 mg/day led to significant improvements in albuminuria and the rate of microalbuminuria resolution over those seen with single-agent valsartan 320 mg/day or lisinopril 40 mg/day.⁵⁹ On the contrary, in the aforementioned ONTARGET study in more than 25,000 patients with atherosclerotic vascular disease or diabetes-related end-organ damage, there was an unexpected worsening in the primary composite outcome (dialysis/SCr doubling/death) with the combination of telmisartan 80 mg/day plus ramipril 10 mg/day compared with either agent alone (hazard ratio 1.09; $P=0.037$).⁹⁸ The placebo-controlled IMPROVE ($n=405$) and telmisartan TRANSCEND studies did not show renal benefits for ARB treatment in patients without microalbuminuria at high risk for CV disease.^{88,97}

Comparative Trials of Losartan Versus Another ARB

Recognizing that differences in AT₁ antagonism across the ARBs may confer renoprotective differences, a small Japanese RCT evaluated the relative merits of perindopril, trandolapril, candesartan, and losartan in 62 hypertensive patients with chronic renal disease, focusing on proteinuria and urinary nitrite/nitrate (NOx) excretion over 96 weeks.¹¹⁸ The four agents were similar in their BP reductions and lack of effect on creatinine clearance. When comparing the ARBs, candesartan was more effective than losartan in reducing proteinuria and was associated with sustained antiproteinuric activity during the study (which was not the case for losartan), with a significant difference between candesartan and losartan at study end. Substantial increases in urinary NOx excretion were likewise seen with all agents, except losartan. Overall, these results suggested that the antiproteinuric effects of losartan are less pronounced than those achieved with an ACEI or candesartan.

Losartan is the only ARB with established uricosuric activity.¹¹⁹ Accordingly, the results of a South African RCT of the effects of losartan compared with candesartan on uric acid, renal function, and fibrinogen in 59 patients with hypertension and diuretic-associated hyperuricemia pointed to advantages in the losartan arm.¹¹⁹ Although BP reductions were similar in the two groups, the losartan group experienced a significant reduction in uric acid levels after 24 weeks and significantly fewer patients had a SCr increase of 10%, compared with the candesartan group (14.2% vs. 44%; $P<0.02$).

Hypothesizing that an ARB with high lipophilicity and long half-life (telmisartan) would be more effective in reducing proteinuria than a low lipophilicity ARB with a shorter half-life (losartan), the AMADEO study ($n=860$) was

conducted using the 52-week difference in the urinary protein/creatinine ratio as the primary endpoint.¹¹⁶ This variable decreased significantly ($P<0.0001$) from baseline to week 52 in both groups; however, the reduction was significantly more pronounced with telmisartan than with losartan (29.8% vs. 21.4%; $P=0.03$), as were the reductions in several secondary outcomes, including CV morbidity/mortality (21 events vs. 37 events; $P=0.037$) and all-cause mortality (two events vs. 13 events; $P=0.007$). A 4.2 mmHg difference in systolic BP was seen at week 8, favoring the telmisartan group; however, differences were much less pronounced at all subsequent time points.

Comment on the Renoprotection Experience With Losartan Versus Other ARBs

Losartan and irbesartan have an established renoprotective role in patients with T2D nephropathy. Experiences with these and other ARBs have been consistent in diabetic renal disease but not in nondiabetic renal disease. Some limited evidence from RCTs suggests greater antiproteinuric effects for candesartan (in chronic renal disease) and telmisartan (in T2D nephropathy) than with losartan, which has uricosuric effects that may benefit patients with hyperuricemia-associated renal disease. The relative impact of losartan compared with other ARBs as renoprotection in diabetic and nondiabetic renal disease is unknown.

Although not the focus of this article, numerous RCTs also support the positive effects of RAAS blockade on the prevention of diabetes (eg, LIFE, SCOPE). Elliott and Meyer conducted a meta-analysis that included 22 RCTs and more than 143,000 patients, most of whom had hypertension.¹²⁰ The antihypertensive class least associated with incident diabetes was the ARBs, with an odds

ratio of incident diabetes of 0.57, compared with diuretics ($P<0.0001$). Further assessment of the role of ARBs in preventing diabetes was addressed in the NAVIGATOR study. This is a large multicenter randomized study with the goal of evaluating the effects of valsartan or nateglinide treatment, individually or combined, on reducing the risk for T2D or CV events in patients with impaired glucose tolerance.¹²¹ Recently published results support a modest but statistically significant 14% reduction in incident T2D with a 5-year course of valsartan versus placebo (33.1% vs. 36.8%; $P<0.001$) but no CV event reduction (14.5% vs. 14.8%; $P=0.43$), with improvement in neither outcome with nateglinide versus placebo.^{122,123}

CLINICAL PRACTICE CONSIDERATIONS

The clinical practice considerations taken from the trials discussed for callout are as follows:

- Efficacy and safety results of any given trial of one particular ARB may not be easily extrapolated to another ARB.
- Switching from one ARB to another solely on the basis of cost, irrespective of the clinical trial data available for the specific agents, can have adverse economic implications.
- For effects beyond BP, there is no accepted method for determining which dose of an unstudied ARB might provide similar effectiveness compared with an ARB that has been proven effective in an RCT (ie, there is no dose-equivalency map).
- When treating patients, clinicians should design a treatment plan that takes into consideration all comorbidities/risk factors and choose the ARB that is proven effective, based on RCTs, in their management.

Losartan was the first commercially available ARB and therefore the first to be available on a generic basis. Although in today's environment of increasing healthcare costs, economic factors play a major role in determining the type of antihypertensive agent prescribed, it is important to also consider clinical evidence from large-scale RCTs in the selection process. Regarding the ARB class of agents, efficacy and safety results of any given trial of one particular agent may not be easily extrapolated to another ARB. Switching from one ARB to another solely on the basis of cost, irrespective of the clinical trial data available for the specific agents, can have adverse economic implications.¹²⁴ For example, in an economic analysis of patients in whom a switch from valsartan to another ARB was prompted by a copayment increase, this nonmedical reason for switching increased the ARB discontinuation rate, hypertension-related outpatient visits, and the number of days of hypertension-related hospitalization, thereby increasing healthcare resource use and costs.¹²⁴ Although RCTs showed differences between ARBs in regard to slowing down the progression in organ damage, data concerning prevention of CV morbidity/mortality are lacking.

Another complicating issue is that, for effects beyond BP, there is no accepted method for determining which dose of an unstudied ARB might provide similar effectiveness compared with an ARB that has been proven effective in an RCT (ie, there is no dose-equivalency map). Although BP control is clearly an important goal of ARB treatment, dosing decisions become more complex when other comorbidities are factored into the equation. In some situations the correlation between BP control and organ protective effects is low, such as in patients with HF (eg, patients with normal BP in Val-HeFT derived benefit from valsartan treatment) or normotensive patients with diabetic nephropathy

(eg, the IRMA-2 study showed benefit from increasing the irbesartan dose, leading to a significant reduction in albuminuria despite small BP differences). Based on the recent results of the HEAAL study ($n=3846$) (not discussed previously herein because of the lack of a non-losartan arm, and the current maximum dose approved for losartan is 100 mg/day), increasing losartan dosing from 50 mg/day to 150 mg/day in ACEI-intolerant patients with HF led to a significant 10% improvement in reduction in the primary endpoint of death or HF-related hospitalization (43% vs. 46%; $P=0.027$).¹²⁵ However, the results were influenced by a significant reduction for the hospitalization component (13% reduction: 6.0% vs. 7.0% per 100 patient-years; $P=0.025$) but not for all-cause mortality (6% reduction: 7.6% vs. 8.2% per 100 patient-years; $P=0.24$), illustrating the complexity of correlating dose and long-term outcomes with ARB treatment. From a safety standpoint, the higher losartan dose resulted in significantly higher incidences of renal impairment (7.1% vs. 4.7%; $P<0.0001$), hypotension (2.9% vs. 2.1%; $P=0.002$), hyperkalemia (2.8% vs. 1.9%; $P=0.0004$), and angioedema (0.08% vs. 0%; $P=0.03$) but not in significantly higher treatment discontinuation rates attributable to these specific events. Accumulating data suggest that using higher-than-conventional doses of ARB treatment may afford renoprotection without producing greater BP reductions or affecting the safety/tolerability profile, compared with established doses.¹²⁶⁻¹²⁸ Significant reductions in albuminuria, compared with conventional antihypertensive dosing, have been reported for irbesartan 900 mg/day compared with 300 mg/day¹²⁶ and valsartan 640 mg/day compared with 160 mg/day¹²⁷ (both studies in patients with T2D and microalbuminuria, the former of 8 weeks and the latter of 30 weeks' duration) and most recently for candesartan 128 mg/day compared

with 16 mg/day (in patients with diabetes-related or diabetes-unrelated persistent proteinuria).¹²⁸ Currently, no further studies evaluate the long-term effects of supramaximal doses of ARBs on organ protection or CV morbidity/mortality. As the ARBs' life cycle nears the end, no long-term studies are planned.

CONCLUSION

When treating patients, clinicians should design a treatment plan that takes into consideration all comorbidities/risk factors and choose the ARB that is proven effective, based on RCTs, in their management. This strategy could facilitate the clinicians' task of managing complicated patients, together with providing cost savings and better patient compliance.

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APPENDIX: LIST OF CLINICAL TRIAL ACRONYMS

AAA	Amlodipine vs. ARB in Atherosclerosis
ADEPT	Addition of the AT ₁ Receptor Antagonist Eprosartan to ACE Inhibitor Therapy in Chronic Heart Failure
AMADEO	Telmisartan vs. Losartan in Hypertensive Type 2 Diabetic Patients with Overt Nephropathy
CAPRAF	Candesartan in the Prevention of Relapsing Atrial Fibrillation
CASE-J	Candesartan Antihypertensive Survival Evaluation in Japan
CATCH	Italian Candesartan Assessment in the Treatment of Cardiac Hypertrophy
CENTRO	Candesartan on Atherosclerotic Risk Factors
CHARM	Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity
CVIP	Cardiovascular Irbesartan Project
DETAIL	Diabetics Exposed to Telmisartan and Enalapril
DIRECT	Diabetic Retinopathy Candesartan Trials
E-COST	Efficacy of Candesartan on Outcome in Saitama Trial
ELITE	Evaluation of Losartan in the Elderly
EPAS	Endothelial Protection, AT ₁ Blockade and Cholesterol-Dependent Oxidative Stress
EUTOPIA	European Trial on Olmesartan and Pravastatin in Inflammation and Atherosclerosis
GISSI-AF	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardio-Atrial Fibrillation
HEAAL	Heart Failure Endpoint Evaluation of Angiotensin II Antagonist Losartan
HKVIN	Hong Kong Study Using Valsartan in IgA Nephropathy
IDNT	Irbesartan Diabetic Nephropathy Trial
IMPROVE	Irbesartan in the Management of Proteinuric Patients at High Risk of Vascular Events
INNOVATION	Incipient to Overt: Angiotensin II Blocker, Telmisartan, Investigation on Type 2 Diabetic Nephropathy
I-PRESERVE	Irbesartan in Heart Failure with Preserved Ejection Fraction
IRMA-	Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria
ISLAND	Irbesartan and Lipoic Acid in Endothelial Dysfunction
JLIGHT	Japanese Losartan Therapy Intended for the Global Renal Protection in Hypertensive Patients
LIFE	Losartan Intervention for Endpoint Reduction
MARVAL	Microalbuminuria Reduction with Valsartan
MITEC	Media Intima Thickness Evaluation with Candesartan Cilxetil
MOSES	Morbidity and Mortality after Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention

NAVIGATOR	Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research
ONTARGET	Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial
OPTIMAAL	Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan
PRoFESS	Prevention Regimen for Effectively Avoiding Second Strokes
RENAAL	Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan
REPLACE	Replacement of Angiotensin-Converting Enzyme Inhibition
RESOLVD	Randomized Evaluation of Strategies for Left Ventricular Dysfunction
ROAD	Renoprotection of Optimal Antiproteinuric Doses
SCOPE	Study on Cognition and Prognosis in the Elderly
SILVHIA	Swedish Irbesartan Left Ventricular Hypertrophy Versus Atenolol
SMART	Shiga Microalbuminuria Reduction Trial
TRANSCEND	Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease
T-VENTURE	Inhibitory Effect of Valsartan against Progression of Left Ventricular Dysfunction after Myocardial Infarction
VALERIA	Valsartan in Combination with Lisinopril in Hypertensive Patients with Microalbuminuria
Val-HeFT	Valsartan Heart Failure Trial
VALIANT	Valsartan in Acute Myocardial Infarction
VIP	Valsartan Inhibits Platelets
VIVALDI	Investigate the Efficacy of Telmisartan versus Valsartan in Hypertensive Type 2 Diabetic Patients with Overt Nephropathy