REVIEW

Cardio classics revisited – focus on the role of candesartan

Maria Leonarda De Rosa

University of Naples Federico II, Department of Cardiology, Naples, Italy

Abstract: Angiotensin II receptor blockers (ARBs) are antihypertensive agents with considerable evidence of efficacy and safety for the reduction of cardiovascular (CV) disease risk in numerous patient populations across the CV continuum. There are several agents within this class, all of which have contributed to various degrees, to this evidence base. The evidence with ARBs continues to accumulate, with ongoing trials investigating their role in additional patient populations, potentially expanding their efficacy across a broad spectrum of CV disease states. Cardiovascular disease (CVD) is a leading cause of death around the world, accounting for approximately 29.2% of total global deaths. Of all the deaths attributed to CVD, approximately 43% are due to ischemic heart disease, 33% to cerebrovascular disease, and 23% to hypertensive and other heart conditions. CVD has been represented as a "CV continuum". This continuum concept can be used to describe CVD in general or in specific vascular beds (eg, coronary artery disease or cerebrovascular disease). This review article will discuss the results of the landmark ARB candesartan clinical trials published over the past decade. The evidence presented spans the entire CV continuum, including the effects of ARBs in at-risk patients, stroke, myocardial infarction (MI), and heart failure (HF), as well as a brief discussion of ongoing trials.

Keywords: candesartan, cardiovascular disease, angiotensin II receptor blockers

Angiotensin II receptor blockers (ARBs) for cardioprotection in at-risk patients

There have been several large comparative clinical trials examining the impact of ARB therapy on cardiovascular (CV) morbidity and mortality in at-risk patients (Table 1).

In the LIFE study, the difference in the composite endpoint was largely driven by a significant difference in stroke between the two groups (25% relative risk reduction [RRR]; adjusted hazard ratio [HR] 0.75, 95% confidence interval [CI]: 0.63–0.89; $P = 0.001$)[1] (Figure 2).

In SCOPE, there was a statistically significant mean difference between the treatment groups in adjusted blood pressure (BP) reduction: 3.2/1.6 mmHg in favor of the candesartan group ($P < 0.001$). While no statistically significant risk reduction for the primary endpoint was observed (RRR: 10.9%; 95% CI: −6.0–25.1, $P = 0.19$), a significant 27.8% RRR for nonfatal stroke ($P = 0.04$) and nonsignificant 23.6% RRR in all stroke ($P = 0.056$) in favor of candesartan were reported.[2]

In the VALUE trial, BP was significantly lower with amlodipine after 1 month (4.0/2.1 mmHg difference compared to valsartan, $P < 0.001$) and after 1 year (1.5/1.3 mmHg difference compared to valsartan; $P < 0.001$).[3–5]

Correspondence: Professor Maria Leonarda De Rosa
University of Naples, Department of Cardiology,
Via Caravaggio 30 80126
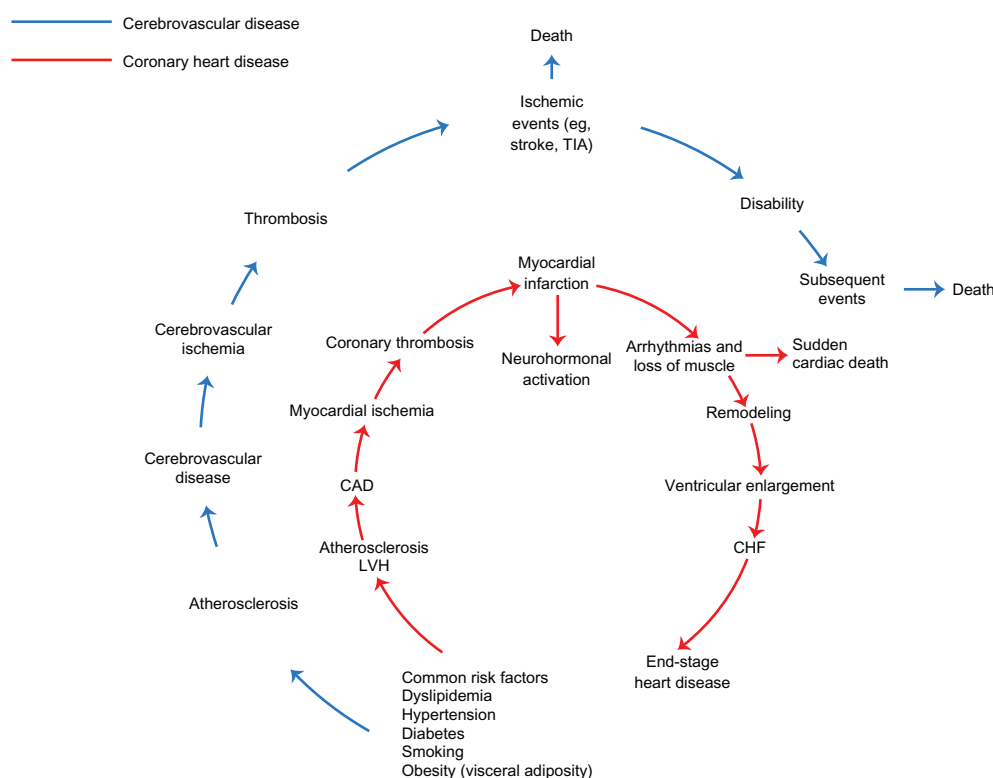Naples, Italy
Email marialeonarda.derosa@unina.it

Figure 1 The CV continuum. Copyright © 2004, Elsevier. Adapted with permission from Julius S, Kjeldsen SE, Weber M, et al; VALUE trial group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet.* 2004;363(9426):2022–2031.
Abbreviations: LVH, left-ventricular hypertrophy; CAD, coronary artery disease; CHF, congestive heart failure; TIA, transient ischemic attack.

Valsartan was further evaluated in the JIKEI-HEART study, the incidence of the composite endpoint was 6.0% in the valsartan group and 9.7% in the non-ARB group, for a RRR of 39% with valsartan (HR 0.61, 95% CI: 0.47–0.79, $P = 0.0002$)[6,7] (Figure 3).

Most recently, two large, parallel studies evaluating the cardioprotective effects of telmisartan have been published: ONTARGET and TRANSCEND trials.[8,9]

ONTARGET demonstrated that telmisartan was non-inferior to ramipril, with no significant difference in the proportion of patients experiencing the primary endpoint (relative risk [RR] 1.01; 95% CI: 0.94–1.09; Figure 4). InTRANSCEND study in the secondary composite endpoint of CV death, mycardial infarction (MI) and stroke, telmisartan therapy was associated with a 13% RRR compared to placebo (HR 0.87, 95% CI: 0.76–1.00, $P = 0.048$ unadjusted.[9]

Effect of ARBs on specific conditions along the CV continuum

The following section documents the efficacy data for ARBs in studies examining more specific patient populations, including those with more advanced disease (eg, post-MI, stroke, and heart failure; Table 1).

Post-stroke

Clinical trial data support the ability of ARBs to prevent stroke in various populations.

In the MOSES study, the reduction in subsequent cerebrovascular events also favored eprosartan (IDR 0.75; 95% CI: 0.58–0.97; $P = 0.03$). BP was similar in both treatment arms at the end of the study.[10]

In the PRoFESS study, 8.7% of patients in the telmisartan group and 9.2% of those in the placebo group had a recurrent stroke (the primary endpoint). However, the between-group difference was not statistically significant (HR 0.95; 95% CI: 0.86–1.04; $P = 0.23$).[11]

Myocardial ischemia and infarction

In the OPTIMAAL study, the investigators reported no significant difference in the primary endpoint between the treatment groups. But it remains unknown whether losartan is noninferior to captopril in this patient population.[12]

In the VALIANT study, in the primary endpoint analysis (all-cause mortality), valsartan met *a priori* defined criteria for non-inferiority compared to captopril (HR 1.00; 97.5% CI: 0.90–1.11; $P = 0.98$) (Figure 5).[13] The VALIANT investigators also included an imputed placebo analysis designed to

Table I Summary of ARB efficacy studies

Study name	Date published	Study drug	Control group(s)	Population studied	Primary endpoint	Primary endpoint results	Statistical significance
Trials in broad (at-risk) patient populations							
LIFE	2002	Losartan	Atenolol	Hypertension and LVH	CV mortality, MI, or stroke	HR: 0.87	95% CI: 0.77–0.98; P = 0.021
SCOPE	2003	Candesartan	Placebo	Older patients (70–89 yrs) with hypertension	CV death, nonfatal stroke or nonfatal MI	RRR: 10.9%	95% CI: -6.0–25.1; P = 0.19
VALUE	2004	Valsartan	Amlodipine	Hypertension and high cardiac risk	First cardiac event	HR: 1.04	95% CI: 0.94–1.15; P = 0.49
JIKEI HEART	2007	Valsartan	Non-ARB antihypertensive therapy	Hypertension, coronary heart disease, HF, or a combination of these disorders	MI; hospital admissions for stroke, TIA, HF or angina; dissecting aneurysm of the aorta; doubling of serum creatinine; or transition to dialysis	HR: 0.61	95% CI: 0.47–0.79; P = 0.0002
ONTARGET	2008	Telmisartan	Ramipril	Vascular disease or high-risk diabetes without HF	MI, stroke, death from CV causes, or hospitalization for HF	RR: 1.01	95% CI: 0.94–1.09
		Telmisartan + ramipril	Ramipril			RR: 0.99	95% CI: 0.92–1.07
TRANSCEND	2008	Telmisartan	Placebo	CVD or diabetes with end-organ damage who were intolerant of ACE inhibitors and who did not have HF	MI, stroke, death from CV causes, or hospitalization for HF	HR: 0.92	95% CI: 0.81–1.05; P = 0.216
Trials in specific patient populations along the CV continuum							
MOSES	2005	Eprosartan	Nitrendipine	High-risk hypertensive patients with a history of a cerebral event	Total mortality and all CV and cerebrovascular events	IDR: 0.79	95% CI: 0.66–0.96; P = 0.014
PRoFESS	2008	Telmisartan	Placebo	Recent history of ischemic stroke	Recurrent stroke	HR: 0.95	95% CI: 0.86–1.04; P = 0.23
OPTIMAAL	2002	Losartan	Captopril	Acute MI and heart failure	All-cause mortality	RR: 1.13	95% CI: 0.99–1.28; P = 0.07
VALIANT	2003	Valsartan	Captopril	Acute MI with HF and/or LV systolic dysfunction	All-cause mortality	HR:1.00	97.5% CI: 0.90–1.11; P = 0.98
		Valsartan + captopril	Captopril			HR: 0.98	97.5% CI: 0.89–1.09; P = 0.73
ELITE II	2000	Losartan	Captopril	HF (NYHA class II–IV) with LVEF ≤ 40%	All-cause mortality	HR 1.13	95.7% CI: 0.95–1.35; P = 0.16
Val-HeFT	2001	Valsartan	Placebo	HF (NYHA class II-IV) with LVEF < 40%	All-cause mortality	RR: 1.02	98% CI: 0.88–1.18; P = 0.80
					Combined mortality and morbidity	RR: 0.87	97.5% CI: 0.77–0.97; P = 0.009

(*Continued*)

Table I (*Continued*)

Study name	Date published	Study drug	Control group(s)	Population studied	Primary endpoint	Primary endpoint results	Statistical significance
CHARM-Added	2003	Candesartan	Placebo	HF: systolic dysfunction who were receiving ACE inhibitors	CV mortality and HF hospitalization	HR: 0.85	95% CI: 0.75–0.96; $P = 0.011$
CHARM-Alternative				HF: systolic dysfunction who were intolerant of ACE inhibitors		HR: 0.77	95% CI: 0.67–0.89; $P = 0.0004$
CHARM-Preserved				HF with preserved LVEF (>40%), with or without background ACE inhibitor use		HR: 0.89	95% CI: 0.77–1.03; $P = 0.118$
I-PRESERVE	2008	Irbesartan	Placebo	HF and preserved LVEF (≥45%).	Death (any cause) or hospitalization for a CV cause	HR: 0.95	95% CI: 0.86–1.05; $P = 0.35$

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; IDR, incidence density ratio; LVH, left ventricular hypertropy; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; RR, relative risk; RRR, relative risk reduction; TIA, transient ischemic attack.
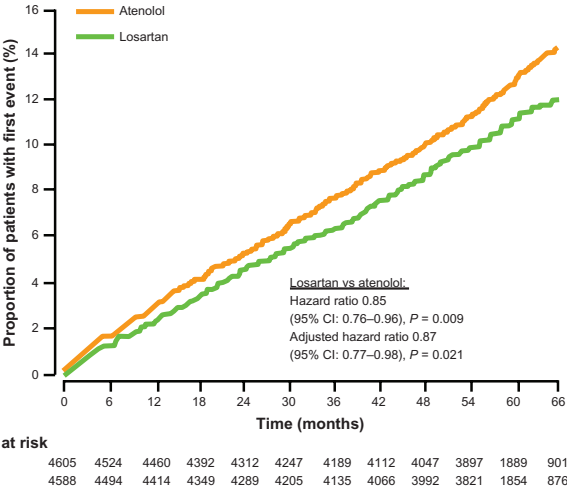

Figure 2 Kaplan-Meier curves for the primary composite endpoint in the life study: losartan vs atenolol in patients with hypertension and LVH. Copyright © 2002, Elsevier. Adapted with permission from Dahlöf B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet.* 2002;359(9311):995–1003.
Abbreviation: CI, confidence interval.

evaluate their findings in the context of the placebo-controlled results of the Survival and Ventricular Enlargement (SAVE) trial, which evaluated captopril,[14] and two other similarly designed ACE inhibitor trials, which tested ramipril and trandolapril in the post-MI setting (the Acute Infarction Ramipril Efficacy [AIRE] trial and the Trandolapril Cardiac Evaluation [TRACE] trial, respectively).[15,16] The two monotherapies were also found to have equivalent effects on other major CV endpoints (eg, MI, stroke).[17]
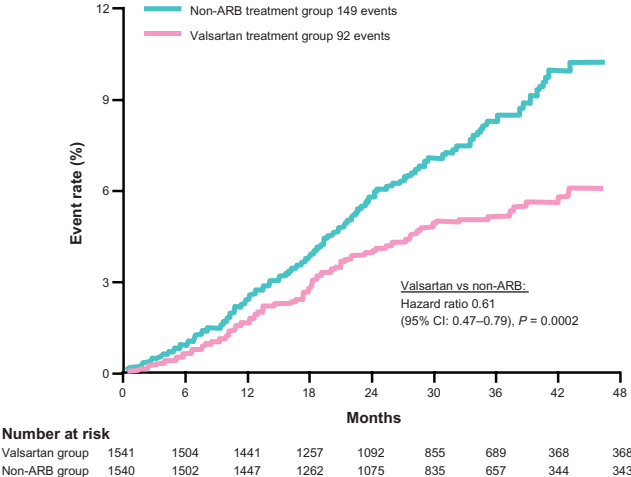

Figure 3 Kaplan-Meier curves of the cumulative frequency of the combined primary endpoint (cv morbidity and mortality) in the jikei heart study: valsartan vs non-ARB treatment. Copyright © 2007, Elsevier. Adapted with permission from Mochizuki S, Dahlöf B, Shimizu M, et al. Valsartan in a Japanese population with hypertension and other cardiovascular disease (Jikei Heart Study): a randomised, open-label, blinded endpoint morbidity-mortality study. *Lancet.* 2007;369(9571):1431–1439.
Abbreviations: ARB, angiotensin II receptor blocker; CI, confidence interval,
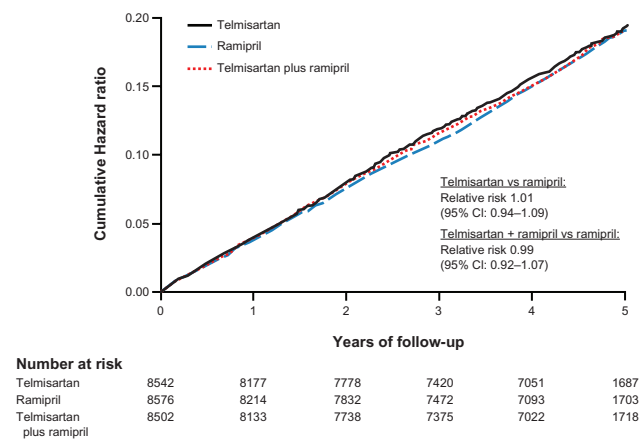
Figure 4 Kaplan-Meier curves for the primary outcome (death from CV causes, MI, Stroke, or hospitalization for HF) in ONTARGET. Copyright © 2008, Massachusetts Medical Society. Adapted with permission from ONTARGET Investigators, Yusuf S, Teo KK, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358(15):1547–1559.
Abbreviations: ONTARGET, Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; CI, confidence interval.

Heart failure (HF)

The ELITE II study[18] sought to validate the findings of ELITE,[19] a study in which low-dose losartan was unexpectedly found to be superior to captopril for the reduction of mortality in patients with HF (a secondary endpoint of ELITE). This trial was designed as a superiority study and was not designed to show equivalence; thus, whether or not an ARB is as protective as an ACE inhibitor in HF remained unanswered by ELITE II.
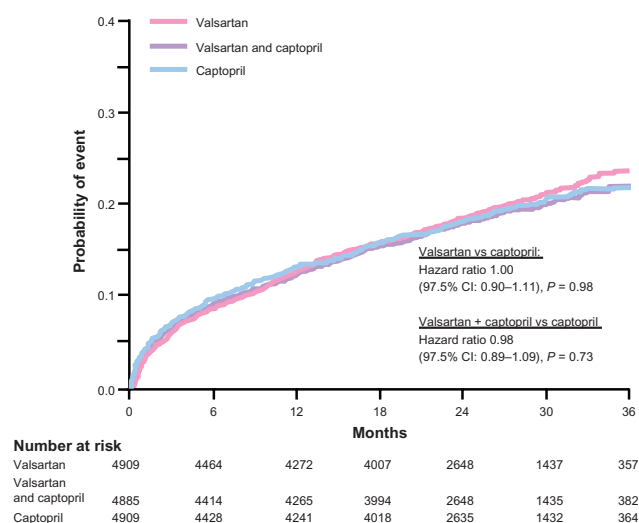
In the Val-HeFT study, there was no significant difference in all-cause mortality between the two treatment arms (RR 1.02; 98% CI: 0.88–1.18; $P = 0.80$).[20]

The Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity (CHARM) study program[21] consisted of a series of separate randomized, controlled studies designed to investigate the benefits of candesartan in three distinct populations of patients with symptomatic HF: those with systolic dysfunction who were receiving ACE inhibitors (CHARM-Added, n = 2,548),[22] those with systolic dysfunction who were intolerant of ACE inhibitors (CHARM-Alternative, n = 2,028)[23] and those with preserved left ventricular (LV) systolic function with or without background ACE inhibitor use (CHARM-Preserved, n = 3,023).[24] The primary objective in each trial was to evaluate the effects of candesartan on the combined primary endpoint of CV mortality or congestive heart failure (CHF) hospitalization.

After a median follow up of 41 months in the CHARM-Added trial, 38% of those in the candesartan group experienced a primary event compared to 42% in the placebo group.[22] The RRR for candesartan (on top of the benefit the patients were already receiving from ACE inhibition) was 15% compared to placebo (unadjusted HR 0.85; 95% CI: 0.75–0.96; $P = 0.011$). The results for each of the components of the primary endpoint were also significantly in favor of candesartan; the RRR was 16% for CV death (unadjusted HR 0.84; 95% CI: 0.72–0.98; $P = 0.029$) and
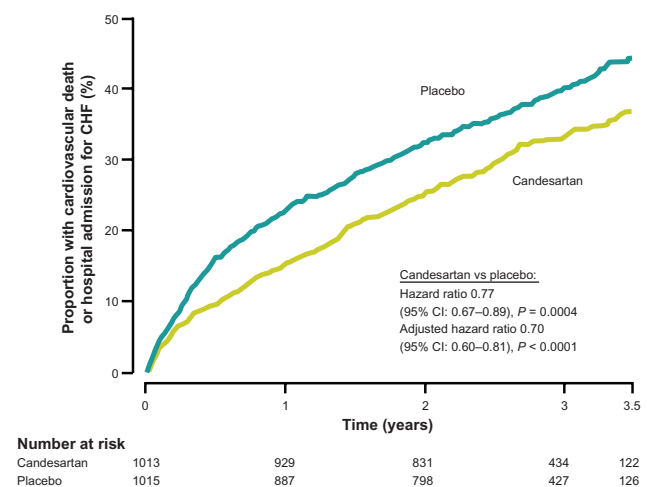

Figure 5 Kaplan-Meier estimates of the rate of death from any cause in the VALIANT Study: valsartan, captopril or their combination in Post-MI patients. Copyright © 2003, Massachusetts Medical Society. Adapted with permission from Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med*. 2003;349(20):1893–1906.
Abbreviations: VALIANT, Valsartan in Acute Myocardial Infarction; CI, confidence interval.

Figure 6 Kaplan-Meier Cumulative Event Curves for the Combined Primary Endpoint (CV Morality + Hospitalization for Heart Failure): Candesartan vs Placebo in ACE-inhibitor-intolerant Patients – CHARM-alternative. Copyright © 2003, Elsevier. Adapted with permission from Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet*. 2003;362(9386):772–776.
Abbreviations: CHARM, Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity; CHF, congestive heart failure; CI, confidence interval.

17% for HF hospitalization (unadjusted HR 0.83; 95% CI: 0.71–0.96; *P* = 0.014). This study further supports the concept introduced by Val-HeFT that adding an ARB to ACE inhibition may provide benefit in patients with HF and systolic dysfunction.

Over a median follow up of 33.7 months in the CHARM-Alternative trial, the RRR for the primary composite outcome was 23% in favor of candesartan (unadjusted HR 0.77; 95% CI: 0.67–0.89; *P* = 0.0004; Figure 6).[23] This finding appears to have been driven primarily by a reduction in HF hospitalizations, for which the RRR was 32% (unadjusted HR 0.68; 95% CI: 0.57–0.81; *P* < 0.0001).

In the CHARM-Preserved study, there was no significant difference in the primary endpoint between the two treatment arms over a median follow up of 36.6 months (unadjusted HR 0.89; 95% CI: 0.77–1.03; *P* = 0.118).[24]

In I-PRESERVE, there was no significant difference in the primary composite outcome between irbesartan and placebo (HR 0.95; 95% CI: 0.86–1.05; *P* = 0.35).[25]

Although ARBs have been shown to be effective for treating patients with established HF, they have not shown such an effect in its prevention.[26]

Ongoing ARB studies

Clinical trials have clearly demonstrated the efficacy of ARBs throughout the CV continuum. Additionally, studies are ongoing investigating the utility of ARBs in several patient populations in which the efficacy of ARBs is currently unknown or inadequately investigated.[27–35]

Table 2 Ongoing ARB trials with primary CV endpoints across the CV continuum

Study name	ARB	Study population	n (approx.)	Primary endpoint(s)	Novelties
ACTIVE-I[27]	Irbesartan	Atrial fibrillation and ≥1 risk factor for stroke	9,000	Composite of CV events (stroke, non-CNS systemic embolism, MI, or vascular death)	
CORAL[28]	Candesartan	Renal artery stenosis	1,080	Composite CV and renal endpoint: CV or renal death, MI, hospitalization for CHF, stroke, doubling of serum creatinine, and need for renal replacement therapy	
KYOTO HEART[29]	Valsartan	High-risk hypertension	3,000	Composite of CV/renal events (stroke, TIA, MI, HF, angina, dissecting aortic aneurysm, lower limb arterial obstruction, emergency thrombosis, transition to dialysis or doubling of serum creatinine)	
NAGOYA HEART[30]	Valsartan	Hypertension with diabetes or impaired glucose tolerance	3,000	Fatal or nonfatal MI, fatal or nonfatal stroke, admission due to CHF, coronary revascularization, sudden cardiac death	
NAVIGATOR[31]	Valsartan	Impaired fasting glucose	9,518	Progression to diabetes; extended CV composite (CV death, nonfatal MI, nonfatal stroke, hospitalization for HF, revascularization or hospitalization for unstable angina); core CV composite (CV death, nonfatal MI, nonfatal stroke, or hospitalization for HF)	
ROADMAP[32]	Olmesartan	Type 2 diabetes with normoalbuminuria	4,400	Occurrence of microalbuminuria (CV morbidity and mortality as secondary endpoint)	
SCAST[33]	Candesartan	Acute stroke	2,500	Death or disability at 6 months; combination of vascular death, myocardial infarction, or stroke during the first 6 months	
VALISH[34]	Valsartan	Isolated systolic hypertension	3,000	Composite of CV events (sudden death, fatal or nonfatal stroke, fatal or nonfatal MI, death due to HF, other CV death, unplanned hospitalization for CV disease, and renal disorder)	
VART[35]	Valsartan	Hypertension	797	CV morbidity and mortality	

Abbreviations: ACTIVE-I, atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events; CORAL, cardiovascular outcomes in renal atherosclerotic lesions; NAGOYA HEART, novel antihypertensive goal of hypertension with diabetes – hypertensive events and ARB treatment; NAVIGATOR, nateglinide and valsartan in impaired glucose tolerance outcomes research; ROADMAP, randomized olmesartan and diabetes microalbuminuria prevention; SCAST, Scandinavian candesartan acute stroke trial; VALISH: valsartan in elderly isolated systolic hypertension; VART, valsartan amlodipine randomized trial; CNS, central nervous system; CV, cardiovascular; MI, myocardial infarction; HF, heart failur; CHF, congestive heart failure; TIA, transient ischemic attack.

These key ongoing studies are summarized in Table 2, along with their significance in the CV continuum. Additionally, there are newer therapeutic approaches to suppress the RAS system through direct renin inhibition. Currently, a comprehensive clinical trial program known as ASPIRE-HIGHER, is evaluating the effects of the direct renin inhibitor, aliskiren, on various CV and cardio-renal endpoints.[36]

Role of candesartan: indications for this angiotensin II receptor blocker
Binding characteristics of the AT1-receptor blockers at the AT1 receptor

Candesartan cilexetil, is administered in an inactive form and is rapidly and completely converted to the active drug, candesartan, during gastrointestinal absorption. *In vitro* studies have shown that candesartan has the highest receptor affinity of all the available AT1-receptor blockers and is not displaced from the receptor by high concentrations of angiotensin II. The tight and long-lasting binding of candesartan to the AT1-receptor provides effective blockade of the negative cardiovascular effects of angiotensin II.

Candesartan reduces the maximal response to angiotensin II, and can almost completely abolish the response; this inhibition cannot be overcome by increasing concentrations of angiotensin II and hence is described as *insurmountable* inhibition.[37,38] It results from fast and reversible binding of the antagonist to the receptor, whereas fully insurmountable inhibition, as with candesartan, is related to slow dissociation of the receptor–antagonist complex.[38] In other studies, reversal of the inhibitory effect of candesartan in CHO cells was slower than with irbesartan or EXP-31748, while the effect of losartan was almost instantaneously reversible, suggesting that insurmountable antagonism is related to prolonged binding of the antagonist to the receptor.[39]

The potent AT1-receptor blockade produced by candesartan and EXP-3174 appears to be related to the presence of two negatively charged groups, a carboxyl group and a tetrazole moiety: the less potent precursors of these molecules, candesartan cilexetil and losartan, possess only the tetrazole moiety.[38] Other potent AT1-receptor blockers also appear to be diacidic molecules.[38] Experiments with candesartan analogues suggest that appropriate alignment of the carboxylgroups is a prerequisite for tight and prolonged binding,and hence for insurmountable antagonism.[38]

Tolerability
The long-term efficacy and tolerability of candesartan cilexetil was assessed in two open-label, prospective multi-centered studies in patients with mild to moderate essential hypertension.[39] Candesartan cilexetil was well tolerated and was devoid of clinically relevant biochemical, hematological or cardiac effects. Only 12% of adverse events were judged to be causally related to the drug and only about 5% of patients withdrew from therapy due to adverse events. The most common adverse events were typical of patients with hypertension in general. Most adverse events appeared during the first 3 months of treatment and their incidence decreased steadily with time. Tolerability was unrelated to gender, age (<65 versus ≥65 years) or dosage. These results demonstrate that candesartan cilexetil maintains its antihypertensive effects and tolerability during long-term administration.[40]

Candesartan does not inhibit ACE, also known as kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin, nor does it bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation. It therefore leads to fewer side effects, particularly the troublesome cough with ACE inhibitors.

Clinical indications
Candesartan is currently licensed for the treatment of hypertension and HF with reduced left ventricular function. However, candesartan may have wider benefits in the treatment of renal disease and diabetic retinopathy.

Hypertension
Candesartan therapy causes a dose-dependent reduction in arterial blood pressure. Systemic peripheral resistance is decreased, while heart rate, stroke volume and cardiac output are not significantly affected.[41] No first dose hypotension was observed during controlled clinical trials with candesartan.

Most of the antihypertensive effect develops within 2 weeks of initial dosing, with a full effect seen by 4 weeks. With once-daily dosing, the BP effect was maintained over 24 hours with trough to peak ratios of more than 80%. As once-daily monotherapy, candesartan cilexetil 8 mg is as effective as enalapril 10–20 mg, amlodipine 5 mg or hydrochlorothiazide 25 mg, and candesartan cilexetil 16 mg is more effective than losartan 50 mg.[42]

The results of a number of head-to-head clinical comparisons between ARBs suggest that candesartan cilex-

etil and irbesartan may be more effective than the losartan.[43] Ambulatory BP studies have clarified the relative duration of antihypertensive action of the AT1 receptor blockers. In particular, studies mimicking the common event of a missed or delayed tablet show that the antihypertensive effect of candesartan cilexetil extends well beyond the 24 h dosing interval, while the effect of losartan declines rapidly over this period.

Candesartan cilexetil has additional BP lowering effects when added to hydrochlorothiazide.[44] Candesartan/hydro-chlorothiazide (CC/HCTZ) combination and amlodipine were equally effective in reducing BP in patients with hypertension not controlled by monotherapy, but CC/HCTZ was better tolerated.[45] After 8 weeks of treatment both regimens reduced mean trough BP by similar amounts: mean sitting SBP/DBP reductions were −15.4/−11.9 mmHg for CC/HCTZ and −15.7/−12.0 mmHg for amlodipine (group differences, $P = 0.835/0.963$). The BP of 84.2% of patients on CC/HCTZ and 84.5% on amlodipine was controlled (sitting DBP < 90 mmHg and sitting SBP < 140 mmHg) ($P = 1.00$). Six (5.9%) patients on CC/HCTZ and 18 (17.6%) on amlodipine discontinued treatment, including one (1%) and 12 (11.8%), respectively, owing to adverse events ($P < 0.001$). The most common adverse event was peripheral edema, which occurred in two patients on CC/HCTZ and 19 on amlodipine. Other trials have confirmed the safety and efficacy of CC/HCZ combination therapy in the treatment of severe hypertension (DBP > 110 mmHg).[46,47]

The tolerability of candesartan was similar in men and women and in patients older and younger than 65.[48] Candesartan was effective in reducing BP regardless of race, although the effect was slightly lower in black (usually a low-renin population) than in white people.[49]

Hypertension endpoint studies

While the data on the antihypertensive benefits of candesartan are compelling in terms of efficacy, there are fewer reported hard endpoint clinical trials. The Study on Cognition and Prognosis in the Elderly (SCOPE) enrolled 4964 patients aged 70–89 years. Patients were randomly assigned to double-blind candesartan or placebo with open-label antihypertensive therapy (mostly thiazide diuretics) added as needed to control blood pressure. Approximately 35% of patients had isolated systolic hypertension (SBP > 60 mmHg, DBP < 90 mmHg). Blood pressure fell by 21.7/10.8 mmHg in the candesartan group and by 18.5/9.2 mmHg in the control group. Candesartan-based therapy was associated with a nonsignificant 10.9% relative risk reduction (242 versus 268

events) in the primary composite endpoint of cardiovascular death, nonfatal stroke and nonfatal myocardial infarction. There were significant reductions in nonfatal stroke (27.8%, $P = 0.04$), and all stroke (23.6%, $P = 0.056$) but no differences in myocardial infarction and cardiovascular mortality in the candesartan-treated cohort. The proportions of patients who had a significant cognitive decline or developed dementia were similar in the two treatment groups.[50] In a predefined subgroup analysis of patients with isolated systolic hypertension, candesartan-based therapy was associated with a 42% risk reduction ($P = 0.049$ adjusted for baseline risk) despite similar BP control (difference between treatments 2/1 mmHg; $P = 0.101$ and 0.064).[51]

The Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) study was a Phase II multicenter double-blind placebo controlled trial designed to assess the safety of modest BP reduction by candesartan cilexetil in the early treatment of stroke.[52] Five hundred patients were enrolled. The trial was stopped prematurely when 342 patients (339 valid) had been randomized because of an imbalance in endpoints. However, the trial reported that, in the absence of blood pressure lowering, candesartan treatment for 7 days, started within 24 hours of motor deficit associated with stoke, reduced the cumulative 12-month mortality rate (7.2 and 2.9% for placebo and candesartan, respectively) and vascular events (18.7 and 9.8% for placebo and candesartan, respectively). Demographic data, cardiovascular risk factors, and BP on admission, on study onset, and within the whole study period were not significantly different between the two groups, nor were there significant differences in concomitant medication and in number or type of side effects. The authors concluded that early initiation of low-dose candesartan was safe in acute stroke, and may provide therapeutic benefits. BP reduction is clearly important in secondary prevention and candesartan is a safe and effective therapeutic option.

These results have not been confirmed in the recently published and much larger PRoFESS trial of another ARB, telmisartan, in the management of acute stroke.[53]

The evidence of added benefit from the use of ARB therapy in patients with recent stroke disease is therefore not compelling at present but further, larger scale, studies on the initiation of ARB therapy within 24 hours of the onset of motor deficit are needed.

Prehypertension

Prehypertension is very prevalent, affecting over 30% of the adult population. The mechanism of elevated risk for cardiovascular events associated with prehyperten-

sion is presumed to be the same as that of hypertension. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[54] emphasizes the importance of lifestyle measures, with weight control and exercise as the mainstay of therapy, except for higher risk people such as those with diabetes, chronic kidney disease, and known coronary artery disease.

The Trial of Preventing Hypertension (TROPHY) study recruited people with 'high normal blood pressure' who were randomized to 4 years of placebo (n = 381) or 2 years of 16 mg/day of candesartan (n = 391) followed by 2 years of placebo. At 2 years, there was a 26.8% absolute and a 66.3% relative risk reduction ($P < 0.0001$) of hypertension in the candesartan-treated group. At study end, the former candesartan group had a 9.8% absolute and a 15.6% relative risk reduction ($P < 0.007$) of hypertension. The treatment was well tolerated. The TROPHY trial is the first trial of pharmacological intervention in people with prehypertension. As such it has stimulated debate about this approach,[55,56] but, since the clinical and financial implications of treating over one third of the adult population are substantial, larger scale clinical outcome trials are needed before this can be widely advocated.

Chronic heart failure

The central role of RAAS system blockade in the treatment of chronic congestive heart failure is well established. There is a large body of endpoint clinical trial data supporting the benefits of ACE inhibitors in heart failure management, with reported reductions of 23% in total mortality, of 35% in a combined endpoint of mortality or hospitalization for heart failure.[57] A recently published meta-analysis of 18,160 patients enrolled in nine trials which met the inclusion criteria reported a 2.3% increased risk of developing any adverse effect ($P < 0.00001$). Risks predictably included hypotension, worsening renal function and hyperkalemia. The authors concluded that ARBs should not routinely be added to ACE inhibitor therapy for left ventricular dysfunction. If chosen in higher risk patients, for example those with ejection fractions below 40% and continued symptoms despite ACE inhibitor and β-blocker therapy,[58] the combination strategy warrants closer patient monitoring to detect adverse effects.

Atrial fibrillation

Further analysis of CHARM results also shows a reduced incidence of atrial fibrillation in patients on candesartan. Of the 7601 patients in the overall CHARM population, 6379 did not have atrial fibrillation at baseline and these patients were included in the new secondary analysis. This showed at a median follow-up of 37.7 months that 5.55% of patients in the candesartan group were reported to have experienced one or more episodes of atrial fibrillation compared with 6.74% in the placebo group ($P = 0.048$). The relative risk reduction for the incidence of atrial fibrillation was 17.7% for candesartan treatment compared with placebo. This reduction was observed across all groups of heart failure.[59] These results are consistent with those from previous trials, which have indicated that ARBs may reduce atrial fibrillation.[60,61]

According to Roland E Schmieder et al RAS inhibition is an emerging treatment for the primary and secondary prevention of AF but acknowledges the fact that some of the primary prevention trials were post-hoc analyses. Further areas of uncertainty include potential differences among specific RAS inhibitors and possible interactions or synergistic effects with antiarrhythmic drugs. In fact the authors reviewed published clinical trial data on the effects of renin-angiotensin system (RAS) inhibition for the prevention of atrial fibrillation (AF), aiming to define when RAS inhibition is most effective; but individual studies examining the effects of RAS inhibition on AF prevention have reported controversial results. Overall, RAS inhibition reduced the odds ratio for AF by 33% ($P < 0.00001$), but there was substantial heterogeneity among trials. In primary prevention, RAS inhibition was effective in patients with heart failure and those with hypertension and left ventricular hypertrophy but not in post-myocardial infarction patients overall. In secondary prevention, RAS inhibition was often administered in addition to antiarrhythmic drugs, including amiodarone, further reducing the odds for AF recurrence after cardioversion by 45% ($P = 0.01$) and in patients on medical therapy by 63% ($P < 0.00001$).[62]

Diabetes prevention

It has been suggested that RAAS blockade may reduce the development of type 2 diabetes by hemodynamic effects, such as improved delivery of insulin and glucose to peripheral skeletal muscle, and nonhemodynamic effects, including direct effects on glucose transport and insulin signaling pathways, all of which decrease insulin resistance.[63] Experimental data using mouse models showed that candesartan prevented deterioration of glucose tolerance by providing protection against progressive β-cell damage in diabetes.[64] One systematic literature search identified 11 trials which enrolled 66,608 patients. ACE inhibitor or ARB therapy was associated with a 22% reduction in new-onset type 2 diabetes.[65] A number

of large clinical trials of RAAS blockade have also reported reductions in new-onset diabetes of between 14 and 34%.[66] A recent meta-analysis was undertaken to assess the effects of antihypertensive agents on incident diabetes. A systematic review identified 48 randomized groups of 22 clinical trials with 143,153 participants who did not have diabetes at randomization and so were eligible for inclusion. The association of antihypertensive drugs with incident diabetes is therefore lowest for ARB and ACE inhibitors, followed by CCB and placebo, β-blockers and diuretics in rank order.[67] The CASE J trial, a large-scale outcome study in Japan comparing the ARB candesartan cilexetil and the CCB amlodipine showed a reduction in new diabetes as a secondary outcome. Pre-specified analysis of new-onset diabetes showed a significant reduction of 36% with candesartan compared with amlodipine (HR, 0.64; 95% CI: 0.43–0.97; $P = 0.030$). Stratified analysis revealed that this effect was greatest in the obese patients (62% risk reduction).[68] A similar effect was noted as a secondary outcome in HIJ-Create, which showed new onset rates of diabetes with candesartan and non-ARB standard therapy as 1.1% and 2.9%, respectively ($P = 0.027$).[69]

With respect to candesartan, CHARM included the development of type 2 diabetes as a secondary outcome in those patients who did not have a diagnosis of diabetes at entry.[53] Patients received candesartan (target of 32 mg once daily) or matching placebo for 2–4 years. One hundred and sixty-three (6.0%) patients in the candesartan group developed diabetes, compared with 202 (7.4%) in the placebo group, a 28% relative risk reduction ($P = 0.020$). The composite endpoint of death or diabetes occurred in 692 (25.2%) and 779 (28.6%) in the candesartan and placebo groups, respectively (HR, 0.86; 95% CI: 0.78–0.95; $P = 0.004$).

A further small study[70] suggests an improved early-phase insulin response in patients with hypertension with impaired glucose tolerance in association with candesartan treatment, which may delay or prevent the development of insulin resistance and diabetes. Patients with hypertension and impaired glucose tolerance were randomly divided into two groups: group A (n = 6), who received 8 mg/day of oral candesartan for 3 months, and controls (n = 6). Before and after administration, a 75 g oral glucose tolerance test was conducted to compare various parameters. No significant differences in age, body mass index (BMI), SBP, DBP, fasting glucose, or fasting immunoreactive insulin were identified between the groups before administration. After 3 months, there were no significant changes in BMI, SBP and DBP for the controls and in BMI and DBP for group A. However, SBP was significantly decreased from 144 ± 2.6 mmHg to

125 ± 4.6 mmHg in group A. Insulinogenic index tended to be slightly decreased for controls, but was significantly increased from 0.32 ± 0.0 to 0.47 ± 0.1 for group A.

While these studies provide support for the hypothesis that RAAS blockade may reduce the development of new-onset diabetes, recent large-scale trials have failed to confirm this. Neither the Diabetes Reduction Approaches with Ramipril and Rosiglitazone Medications (DREAM) trial with the ACE inhibitor ramipril, in which new-onset diabetes was a primary endpoint, nor the very large ONTARGET found any benefit of ACE inhibitor or ARB therapy in the development of diabetes. The Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial with valsartan is currently ongoing.[71,72]

There is currently insufficient evidence to support the hypothesis that RAAS blockade with candesartan or other ARBs or ACE inhibitors has a significant effect on the development of diabetes.

Urinary albumin excretion

RAAS system blockade is accepted as a central management strategy in the treatment of proteinuric renal disease. RAAS is believed to have a major influence on intraglomerular filtration pressure by preferentially regulating post-glomerular efferent arteriolar resistance leading to intra-glomerular hypertension and the potentiation of proteinuria.[73] Early clinical trials in patients with type 1 diabetes and established renal disease confirmed that an ACE inhibitor based treatment strategy halved the rate of renal deterioration, the need for dialysis and death.[74] Studies have also confirmed the benefits of ACE inhibition at the earlier microalbuminuric stage of diabetic nephropathy[75] and also in the progression of normo- to microalbuminuria.[76] In type 2 diabetes the IDNT[77] and RENAAL[78] trials confirm the renal benefits of irbesartan- and losartan-based therapies in patients with established renal disease, and IRMA-II data[79] confirmed benefit in patients with type 2 diabetes and microalbuminuria. Whether ACE inhibitors or ARBs are superior is a matter of controversy. A Cochrane review in 2004 concluded that the renal benefits of these agents were similar but there were insufficient data to determine whether the ARBs had similar survival benefits to ACE inhibitor therapy.[80] No cardiovascular outcome benefits were seen in the IDNT, IRMA2 and RENAAL trials.

As a potent long-acting ARB, candesartan would be expected to reduce urine protein excretion in a variety of renal diseases. Early studies in rats suggested beneficial reno-protective effects of candesartan[81] and an early comparative trial between candesartan and ACE inhibition confirmed

improvements in proteinuria, with a greater effect seen in the candesartan group.[82]

Murayama and colleagues[83] reported the benefits of candesartan in patients with early kidney disease independent of its antihypertensive effect. Fifty-two patients with type 2 diabetes with normo- or microalbuminuria participated. Nineteen patients with high normal and mild hypertension received low-dose candesartan (4 mg once daily; candesartan group), and 33 patients did not receive candesartan (control group). Blood pressure, urinary albumin excretion, transferrin, and type IV collagen (expressed as urinary creatinine index) and plasma parameters were determined at baseline and at 2, 6, 12 and 18 months after the start of candesartan therapy. Baseline parameters were similar in both groups. Candesartan treatment decreased the higher baseline SBP to the level of the control group. In the control group, urinary albumin excretion increased significantly at 18 months compared with baseline, while no changes in urinary albumin excretion were reported in the candesartan group.

The antiproteinuric effects of candesartan are dose dependent. In a short-term study of 23 patients with hypertension, type 2 diabetes and nephropathy the effect of four treatment doses of 8, 16 or 32 mg candesartan compared with placebo were compared during four treatment periods each lasting 2 months. The trial was double blind and patients received treatment doses in random order. All three candesartan doses significantly reduced albuminuria and 24-hour BP compared with placebo. Mean (95% CI) reductions in albuminuria were 33% (21–43), 59% (52–65), and 52% (44–59) for the 8, 16 and 32 mg dosing schedules, respectively. Higher doses (16 and 32 mg) were associated with a significantly greater antiproteinuric effect, but there were no differences in reduction of BP between the three doses.[84]

Several studies have investigated whether supra-maximal doses of candesartan may have additional effects to reduce proteinuria. In a pilot study in 2004, Weinberg and colleagues[85] reported benefits from doses up to 160 mg daily, which is five times higher than the maximal recommended dose. No safety or tolerability issues were reported. A significant relative reduction of 30% was reported using a 64 mg daily dose of candesartan in 32 patients with diabetic or nondiabetic renal disease when compared with 16 mg daily dosing.[86] Finally, a recent report suggests there are benefits of using supramaximal doses of candesartan in reducing proteinuria.[87] Reductions of 33% were seen using doses of 64 and 128 mg daily compared with 16 mg daily in a trial of 269 patients, mostly with diabetic nephropathy. Whether these reductions are associated with improved long-term renal protection is unknown.

Although much interest has focused on the prevention and treatment of diabetic renal disease, the antiproteinuric effects of candesartan have also been reported in patients with nondiabetic renal diseases, including chronic glomerulonephritis,[88] renal transplant recipients[89] and patients with adult polycystic kidney disease.[90]

Dual blockade using ACE inhibitors and ARBs in combination has received considerable interest over the last 10 years. The Candesartan and Lisinopril Microalbuminuria (CALM) trial first reported improved control of blood pressure and reduced proteinuria using this combination.[91] CALM was a randomized double-blind trial in 199 patients aged 30–75 years with type 2 diabetes, microalbuminuria (urinary albumin: creatinine ratio 2.5–25 mg/mmol), and DBP between 90 and 110 mmHg. Patients were allocated to one of four groups: candesartan for 24 weeks (n = 66), lisinopril for 24 weeks (n = 64), candesartan for 12 weeks with the addition of lisinopril for a subsequent 12 weeks (n = 34), or lisinopril for 12 weeks with the addition of candesartan for a subsequent 12 weeks (n = 35). At 24 weeks, mean DBP was lower with combination treatment (16.3 mmHg) than with candesartan (10.4 mmHg; $P = 0.003$) or lisinopril monotherapy (10.7 mmHg; $P = 0.005$). Similar benefits were seen in SBP with combination treatment. Combination treatment was associated with a greater mean reduction from baseline in urinary albumin to creatinine ratio than candesartan alone (50% versus 24%; $P = 0.04$) but not lisinopril alone (50% versus 39%; $P > 0.20$). Since this early report several small, short-term studies have reported similar benefits.[92–94] More recently the CALM-2 trial[95] did not find any difference between lisinopril 40 mg daily compared with lisinopril 16 mg daily plus the addition of candesartan 16 mg daily during a 12-month follow-up period. Urinary albumin excretion remained stable through the follow-up period in both groups, with no significant differences between the two regimens.

The problem with these studies is their short follow-up, small numbers of study participants and the use of surrogate markers (BP and urine albumin secretion) rather than clinically relevant hard endpoints.

Taken together these data cast significant doubt on the utility of dual RAAS blockade using ACE inhibitors and ARBs, particularly in patients with low-level (<1G per day) proteinuria. In patients with high-range proteinuria, the addition of candesartan to ongoing ACE inhibitor treatment may be considered, but patients on this combination would require careful

monitoring of BP, serum potassium, proteinuria and renal function to ensure safety.

Retinopathy

The growing evidence of local RAAS within the eye which is activated in diabetes, combined with the reported benefits of the ACE inhibitor lisinopril in retinopathy in the EUCLID trial, formed the rationale for the Diabetic Retinopathy Candesartan Trials (DIRECT) clinical trial programme. Local RAS is believed to be responsible, either directly or via other mediators, for increased concentrations of vascular endothelial growth factor, a selective angiogenic and vasopermeability factor implicated in the pathogenesis of diabetic retinopathy.

It has been suggested that inhibition of ACE or blockade of angiotensin II could reduce vascular endothelial growth factor concentrations and favourably influence the development or progression of retinopathy.

The DIRECT programme was designed to assess whether candesartan could reduce the incidence and progression of retinopathy in type 1 diabetes and the progression of retinopathy in type 2 diabetes. The programme consisted of three randomized, double-blind, parallel-design, placebo-controlled trials; two in patients with type 1 diabetes and a third in patients with type 2 diabetes. The DIRECT-Prevent 1 trial recruited participants with normotensive, normoalbuminuric type 1 diabetes without retinopathy. Participants with type 1 diabetes and existing mild–moderate retinopathy were recruited to DIRECT-Protect 1. Participants were assigned to candesartan 16 mg once a day or matching placebo. After 1 month the dose was doubled to 32 mg. The primary endpoints were incidence and progression of retinopathy and were defined as at least a two-step and at least a three-step increase on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale, respectively. New retinopathy developed in 178 (25%) participants in the candesartan group versus 217 (31%) in the placebo group. Progression of retinopathy occurred in 127 (13%) participants in the candesartan group versus 124 (13%) in the placebo group. Hazard ratio (HR for candesartan vs placebo) was 0.82 (95% CI: 0.67–1.00; $P = 0.0508$) for incidence of retinopathy

and 1.02 (95% CI: 0.80–1.31; $P = 0.85$) for progression of retinopathy.

Final ETDRS level was more likely to have improved with candesartan treatment in both DIRECT-Prevent 1 (OR, 1.16; 95% CI: 1.05–1.30; $P = 0.0048$) and DIRECT-Protect 1 (OR, 1.12; 95% CI:1.01–1.25; $P = 0.0264$). The investigators hypothesized that candesartan reduces the incidence of retinopathy, although they did not see a beneficial effect on retinopathy progression in type 1 diabetes.[96]

The DIRECT-Protect 2 programme studied people with type 2 diabetes and retinopathy at enrolment. The study examined whether candesartan treatment could slow the progression and, secondly, induce regression of retinopathy.

Patients with type 2 diabetes who were normoalbuminuric, normotensive or treated hypertensive with mild to moderately severe retinopathy were recruited and assigned to candesartan 16 mg once a day or placebo which was subsequently increased to 32 mg.

A total of 161 (17%) patients in the candesartan group and 182 (19%) in the placebo group had progression of retinopathy by three steps or more on the ETDRS scale. The risk of progression of retinopathy was nonsignificantly reduced by 13% in patients on candesartan compared with those on placebo (HR, 0.87; 95% CI: 0.70–1.08; $P = 0.20$). Regression on active treatment was increased by 34% (HR, 1.34; 95% CI: 1.08–1.68; $P = 0.009$). An overall change towards less severe retinopathy by the end of the trial was observed in the candesartan group (OR, 1.17; 95% CI: 1.05–1.30; $P = 0.003$).

Hence the investigators suggested that treatment with candesartan in patients with type 2 diabetes and mild to moderate retinopathy might induce improvement of retinopathy.[97]

The DIRECT trial programme provides reassurance on the long-term safety of candesartan in a large patient population, with no reported differences between treatment groups.

My evidence

In a recent my paper a population of 154 patients aged 40 to 66 years, was studied, with WHO I-II stage essential hypertension, and electrocardiographic left ventricular

Table 3 Functional capacity at the various treatment steps (mean ± SD)

	Pl	Pl + Asp	Can	Can + Asp
Oxygen consumption at peak exercise (ml/min/kg)	15 ± 3.5	14 ± 5.6	17 ± 3.2*	17.1 ± 3.1*
Dead space/Tidal volume ratio	0.21 ± 0.03	0.22 ± 0.06	0.18 ± 0.04*	0.18 ± 0.04*
Exercise tolerance time(s)	514 ± 186	515 ± 132	580 ± 169*	602 ± 26*

Notes: *Difference from Pl and from Pl+Asp is significant at $P < 0.01$. Copyright © 2009, John Wiley and Sons. Reproduced with permission from De Rosa ML, Chiariello M. Candesartan improves maximal exercise capacity in hypertensives: results of a randomized placebo-controlled crossover trial. *J Clin Hypertens.* 2009;11(4):192–200.
Abbreviations: Pl, placebo; Asp, aspirin; Can, candesartan.

Table 4 Maximal exercise blood pressure and heart rate and oxygen reserve and LVM at the various treatment

Steps (mean ± SD)	PI	PI + Asp	Can	Can + Asp
Maximal systolic BP (mmHg)	202 ± 4	203 ± 4	192 ± 5*	190 ± 4*
Δ systolic BP	55 ± 4	56 ± 3	58 ± 5	58 ± 4
Maximal diastolic BP (mmHg)	99 ± 5	92 ± 2	85 ± 3*	78 ± 2*
Δ diastolic BP	5 ± 5	5 ± 4	6 ± 3	6 ± 4
Maximal Heart Rate (b/min)	161 ± 4	166 ± 2	170 ± 5*	176 ± 3*
Δ Heart Rate	84 ± 4	84 ± 3	96 ± 4*	98 ± 4*
VO2 rest/mass (ml/kg/min)	4 ± 3	4 ± 2	4 ± 4	4 ± 1
LV mass (g)	170 ± 4	170 ± 8	169 ± 2*	169 ± 3*
Oxygen reserve (ratio)	3.8 ± 0.3	3.5 ± 0.2 4	3 ± 0.4*	4.3 ± 0.1*
Δ effort (Borg scale)	19 ± 0.3	19 ± 0.2	19 ± 0.4	19 ± 0.2

Notes: Δ = change with exercise *Difference from PI and from PI + Asp is significant at $P < 0.01$. Copyright © 2009, John Wiley and Sons. Reproduced with permission from De Rosa ML, Chiariello M. Candesartan improves maximal exercise capacity in hypertensives: results of a randomized placebo-controlled crossover trial. *J Clin Hyperten*s. 2009;11(4):192–200.[98]

hypertrophy. They were randomized to receive placebo, candesartan (32 mg), each of these plus aspirin (300 mg/day), or the same preparations in a reverse order, each for 3 weeks, with a 3-week wash out period between treatments. Maximal workload and oxygen reserve were measured cardiopulmonary exercise test, 24-hour ambulatory BP, LV mass index by echocardiography according to American Heart Association recommendations, at the end of each treatment.

The patients did not achieve the maximal workload as predicted by age, gender and weight and height [116 (99–133) vs 132 (116–149) Watts, $P = 0.01$]. This impaired exercise capacity, calculated as the ratio between achieved and predicted maximal workload was in multiple regression analysis related to lower oxygen reserve (r = 0.49, $P < 0.001$), and the lower oxygen reserve to higher *echo* LVH (β = −0.34), respectively.

Candesartan alone or with aspirin caused an improvement of VO2 and exercise tolerance, which was absent in controls (Tables 3–4).

Considering that hypertrophy and remodeling in patients with untreated hypertension have been associated with impaired exercise capacity, candesartan was tested to see whether it improved exercise peak oxygen volume (VO2) in this population.

Thus, hypertensives cannot achieve the predicted maximal workload. This impaired exercise capacity was related to lower oxygen reserve while peak VO2 may be (NYHA class) the strongest prognostic factor in this population.

Furthermore, candesartan may represent an alternative or even an advancement in hypertensives for its efficacy on exercise VO2 and exercise tolerance, without antagonism by aspirin.[98]

Conclusions

Candesartan has shown benefit in the treatment of hypertension. It has been shown to be more effective than losartan[43] in a number of studies. Candesartan has also shown effectiveness when combined with hydrochlorothiazide and good tolerability in this setting.[45] This combination has been shown to be both safe and effective in the treatment of severe hypertension.[46,47]

As well as showing reduction in blood pressure, candesartan has also shown benefits in terms of hypertension endpoint studies. SCOPE showed significant reductions in nonfatal stroke (27.8%; $P = 0.04$) and all stroke (23.6%; $P = 0.049$).[51] ACCESS looked at the early initiation of candesartan following stroke. This trial reported that, despite the absence of BP lowering, candesartan treatment for 7 days, started within 24 hours of motor deficit associated with stoke, reduced the cumulative 12-month mortality rate (7.2 and 2.9% for placebo and candesartan, respectively) and vascular events (18.7 and 9.8% for placebo and candesartan, respectively).[52]

Candesartan has also been studied in the prevention of hypertension in the setting of prehypertension. TROPHY is the first such trial in this group of patients. It showed a 9.8% absolute and a 15.6% relative risk reduction ($P < 0.007$) of hypertension. As this is the first such trial, others will be required to further validate this approach but the implications are far reaching.[55,56]

One of the major areas of importance for candesartan is in the treatment of heart failure, with a reduced ejection fraction below 40%. CHARM showed reduction in cardiovascular death and congestive heart failure hospitalization versus placebo when both used as an alternative to ACE inhibitor therapy (HR = 0.7; $P < 0001$) or when added to ACE inhibitor therapy (HR = 0.85; $P < 0.01$).[58] Interestingly, CHARM also

showed that candesartan reduced the incidence of new atrial fibrillation.[59]

Candesartan has shown a benefit in diabetes prevention. Both the CASE trial and HIJ-Create have shown a reduction in new incidence of diabetes in patients using candesartan. CASE-J showed a significant effect when compared with amlodipine (HR, 0.64; 95% CI: 0.43–0.97; $P = 0.030$) and HIJ-Create showed reduced incidence compared with non-ARB treatment ($P = 0.027$).[67,68]

Data also support its use in patients with proteinuric renal disease as an alternative should an ACE inhibitor not be tolerated, although it should be remembered that it does not have a specific licence for this indication. ARBs have been shown to be beneficial in patients with established renal disease (RENALL, IDNT) and have shown similar benefits to ACE inhibitor therapy.[77,78] Dual blockade using both ACE inhibitors and ARBs has been tried. CALM showed a larger reduction in BP with the combination of candesartan and lisinopril than with monotherapy (13.3 mmHg combination; 10.4 mmHg, $P = 0.003$ candesartan; 10.7 mmHg, $P = 0.005$ lisinopril). There was a reduction from baseline in urinary albumin to creatinine ratio when candesartan was used in combination versus alone (50% versus 24%; $P = 0.04$).[91]

The recent DIRECT study supports the use of candesartan in patients with early stage retinopathy. Candesartan reduced the incidence of retinopathy in DIRECT-Prevent 1. DIRECT Protect 2 showed a change towards less severe retinopathy in the candesartan group versus the placebo group (OR, 1.17; 95% CI: 1.05–1.30; $P = 0.003$).[96,97]

Overall candesartan is a very safe, well tolerated drug from the group of ARBs. Its pleiotropic effects ensure that it has wide-ranging implications for clinical use with an ever expanding wealth of evidence to support its ongoing and widening usage.

Hypertensives had lower measures of peakVO2, oxygen reserve and heart rate at maximal exercise than predicted by age, gender, weight and height.

In my crossover and placebo-controlled study in patients with mild to moderate hypertension, candesartan mono therapy produces a significantly lower arterial BP than placebo or placebo plus aspirin at week 3 of treatment while a combination of candesartan and aspirin yielded a better physical performance and exercise oxygen uptake compared with either drug alone. Furthermore, candesartan may represent an alternative in hypertensive patients for its efficacy on exercise peak VO2 and exercise tolerance, because of similar efficacy of ACE inhibitor for exercise performance and less exposure to the counteracting activity of aspirin.[98]

ARBs have established themselves as versatile agents for the treatment of a variety of conditions throughout the CV continuum. While the accumulation of evidence with ARBs has involved clinical trials with a number of different individual agents, in addition to candesartan, other ARBs such as valsartan, telmisartan, and losartan have demonstrated benefits on major CV endpoints. Pharmacological studies have highlighted the differences among AT1-receptor blockers, and confirmed the tight receptor binding and long-acting properties of candesartan.

Disclosure

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