Angiotensin II Receptor Blockers in high-risk patients

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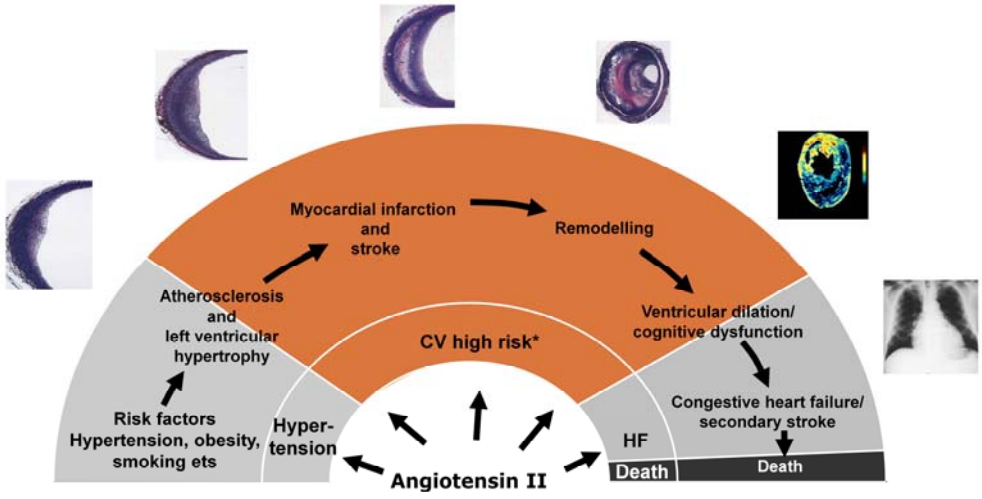
Contents

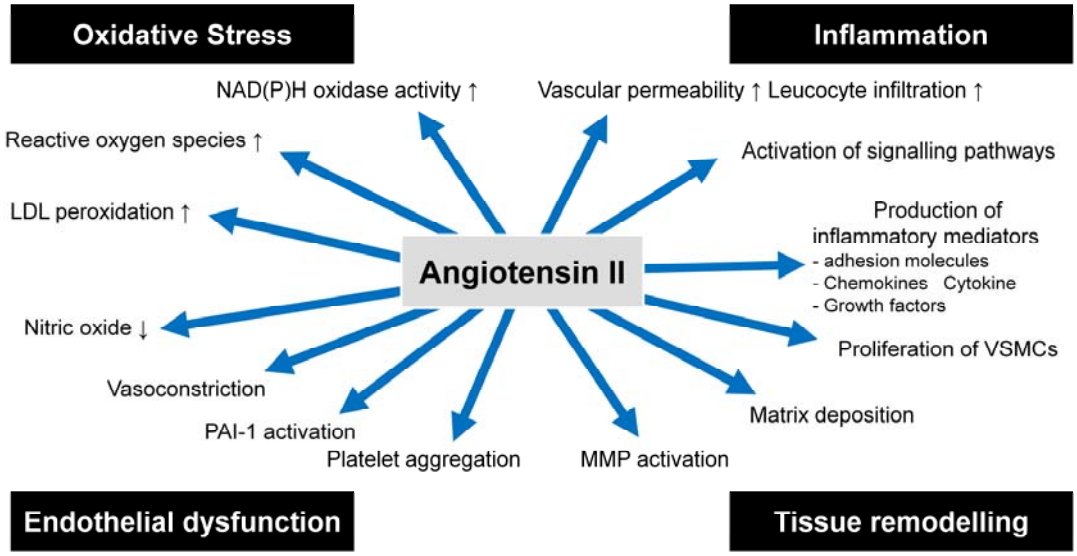
- RAS in cardiovascular diseases
- RAS blockade; randomized trials
- RAS blockade; KAMIR data

Cardiovascular disease progression



Adapted from Dzau VJ, et al. Circulation 2006;114:2850–2870;
Figure adapted from Dzau V, Braunwald E.
Am Heart J 1991;121:1244–1263; Yusuf S, et al. Lancet 2004;364:937–952
EHJ 2007;28:1462

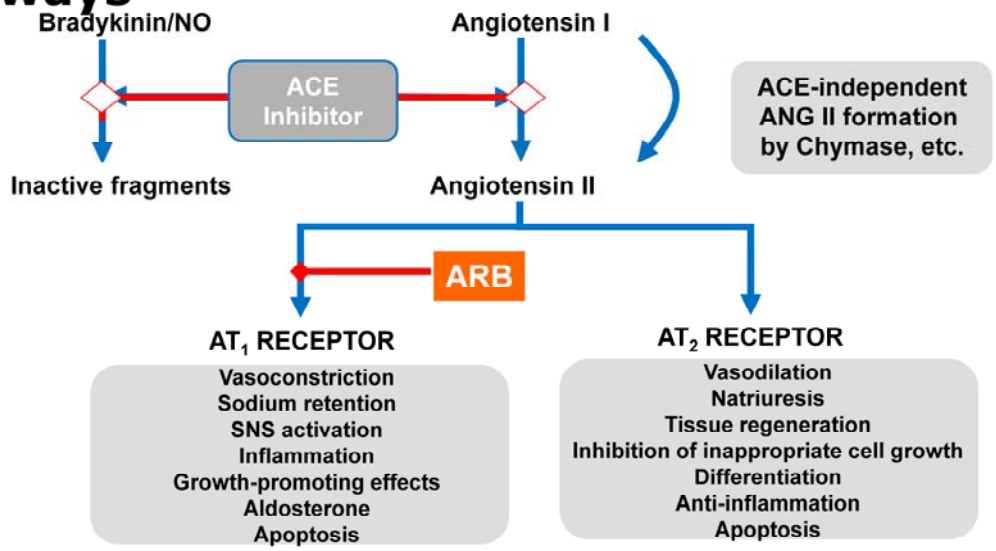
Angiotensin II is important to atherosclerotic mechanisms



VSMCs : Vascular smooth muscle cell, MMP: matrix metalloproteinases, PAI-1 : Plasminogen activator inhibitor ,

Schmieder et al. Lancet 2007;369:1208–1219

ACEI and ARBs block the renin–angiotensin system (RAS) in different ways



ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker;
AT = angiotensin; SNS = sympathetic nervous system

Schmieder et al. Lancet 2007;369:1208–1219
Chen R, et al. Hypertension 2003;42:542–547; Hurairah H, et al. Int J Clin Pract 2004;58:173–183;
Steckelings UM, et al. Peptides 2005;26:1401–1409

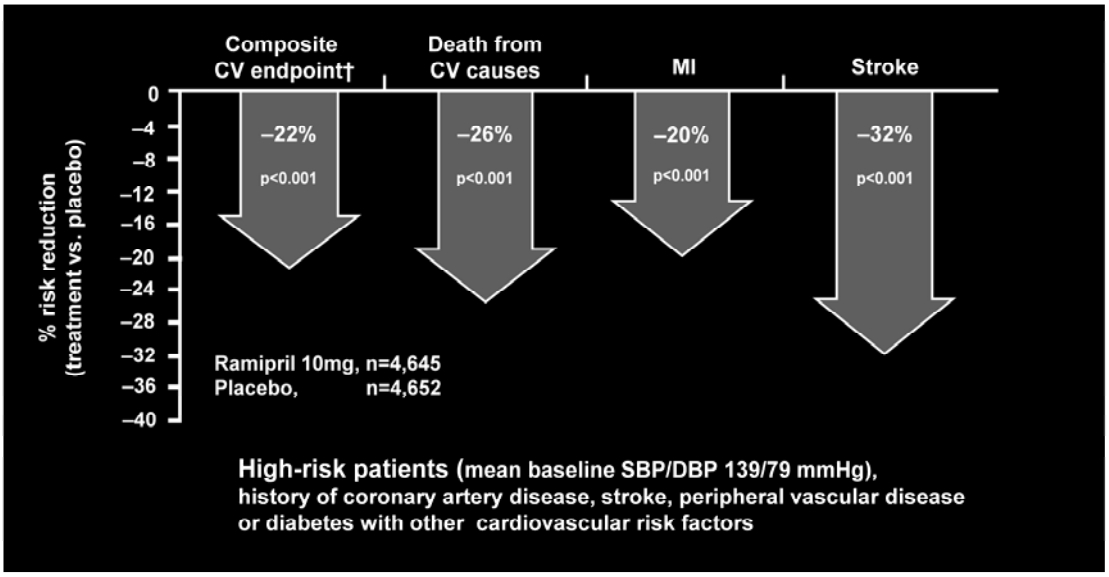
RAS blockade with ACE inhibitors

ACE-Inhibitors reduce CV events* in patients with HF or LV systolic dysfunction

Study	Year	Patients (n)	CV Death, MI, Stroke Odds reduction (95% CI)	p-value
SOLVD-T†	1991	2,569	23% (10-33%)	0.0009
SOLVD-P†	1992	4,228	15% (2-27%)	0.0252
SAVE†	1992	2,231	20% (4-33%)	0.0168
AIRE†	1993	1,986	24% (7-39%)	0.0068
TRACE†	1995	1,749	25% (9-33%)	0.0028
HOPE	2000	9,297	25% (16-32%)	0.0001
EUROPA	2003	12,218	19% (8-28%)	0.0007
PEACE	2004	8,290	7% (-8%-19%)	0.328

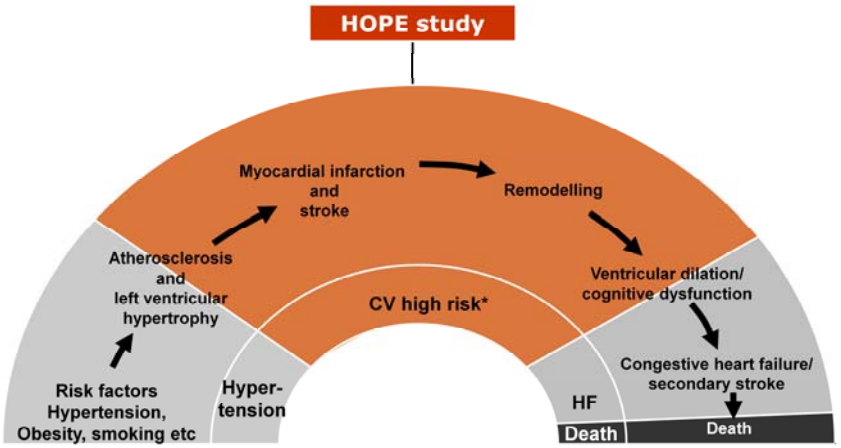
* 3-fold composite CV endpoint: Death, MI, Stroke
† All deaths instead of CV deaths
Dagenais et al. Lancet 2006;368:581–88

Ramipril reduces CV mortality and morbidity beyond BP lowering (HOPE study)



† Composite CV endpoint = death from CV causes + MI + stroke, Mean 3.5 year follow-up
HOPE = Heart Outcomes Prevention Evaluation
Yusuf S, et al. N Engl J Med 2000;342:145–153

The HOPE study showed the effect of ramipril in CV high-risk patients in the middle of the CV continuum



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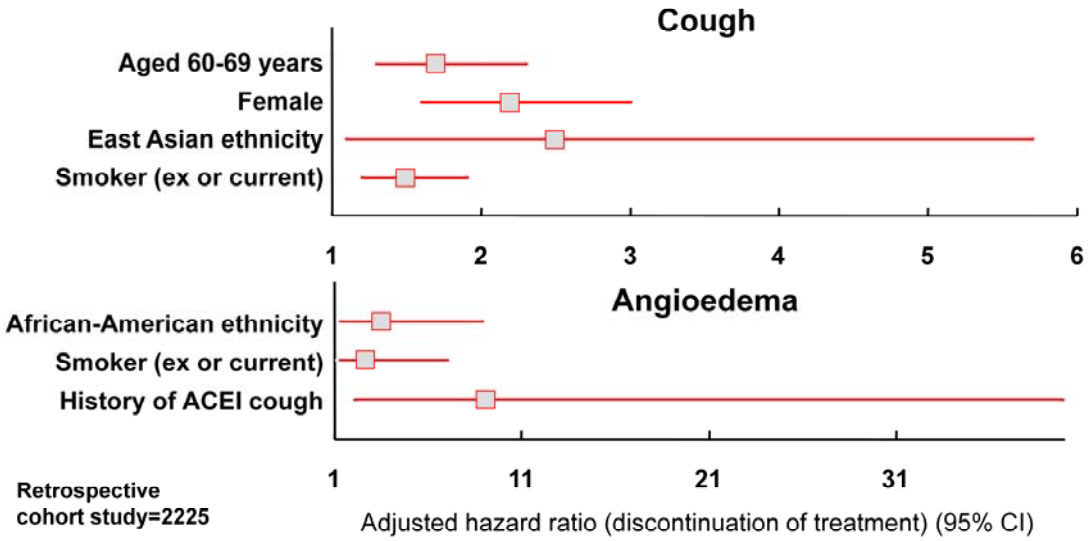
* history of coronary artery disease, stroke, peripheral vascular disease or diabetes with other cardiovascular risk factors

Adverse effects of ACE inhibitor therapy limit tolerability and increases non-adherence

- Cough affects up to 35% of patients treated with ACE inhibitors[1]
- Angio-edema affects 0.2% of patients receiving ACE inhibitors[2,3]
  - *Immediate discontinuation of treatment is essential*

1. Dicpinigaitis PV. Chest 2006;129(Suppl 1):169S-173S
2.Miller DR, et al. Hypertension 2008;51:1624-1630
3. Weber MA, & Messerli FH. Hypertension 2008;51:1465-1367.

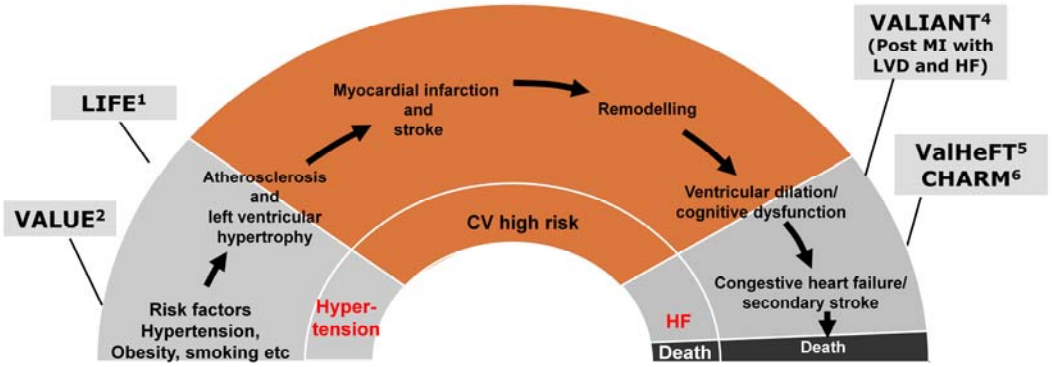
Who is at greatest risk of ACEI adverse events related with discontinuation?



Morimoto et al. J Eval Clin Practice 2004;10:499-509

RAS blockade with ARBs

ARBs had no evidence and indication in CV high risk patients before ONTARGET trials



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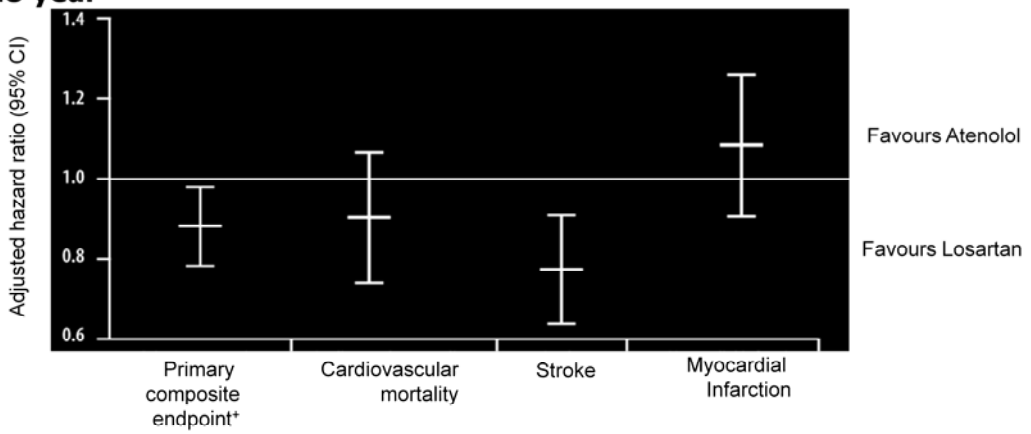
1.Lancet 2002;23:995-1003, 2. Lancet 2004;363:2022-31, 3. N Engl J Med 2008;358:1547-59, 4. N Engl J Med 2003;349:1893-906, 5.N Engl J Med 2001;345:1667, 6. Lancet 2003;362:759-66

Cardiovascular effects of losartan

: mainly from stroke reduction

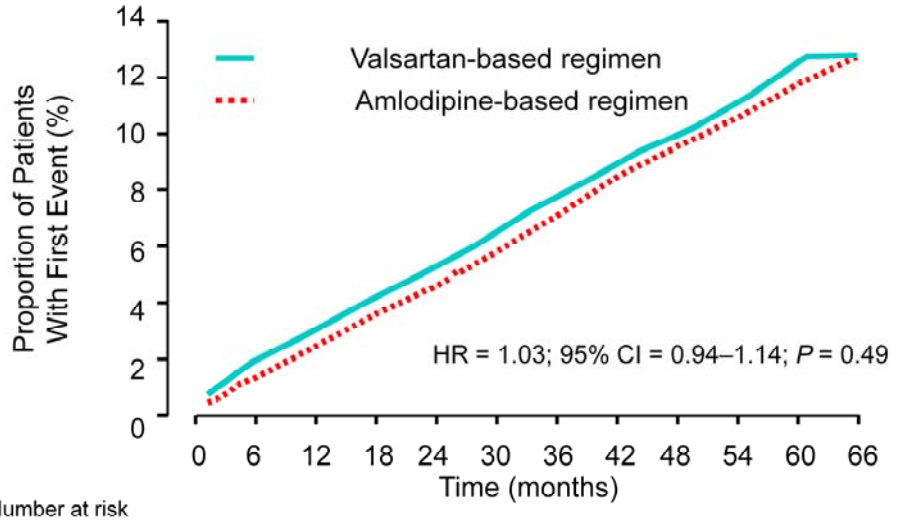
LIFE study: Losartan (n=4,605) vs. atenolol (n=4,588), mean follow-up 4.8 year



LVH : Left Ventricular hypertrophy
+ Cardiovascular mortality, Stroke, Myocardial infarction
Dahlöf B., *et al*. Lancet 2002;359:995–1003

VALUE: Primary Composite Endpoint

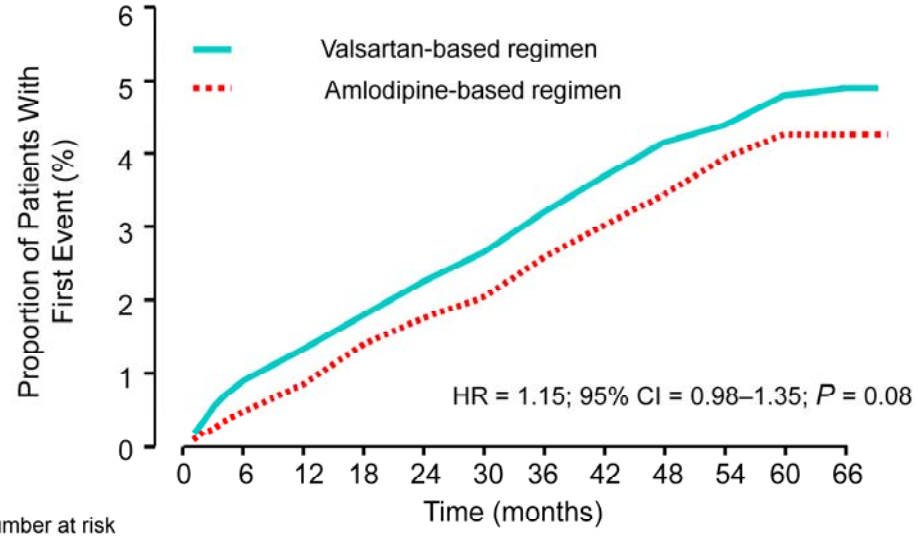
Hypertensive patients with high risk of CV event, mean follow-up 4.2 years



Number at risk												
Valsartan	7649	7459	7407	7250	7085	6906	6732	6536	6349	5911	3765	1474
Amlodipine	7596	7469	7424	7267	7117	6955	6772	6576	6391	5959	3725	1474

Julius S et al. *Lancet*. June 2004;363:2022–31.

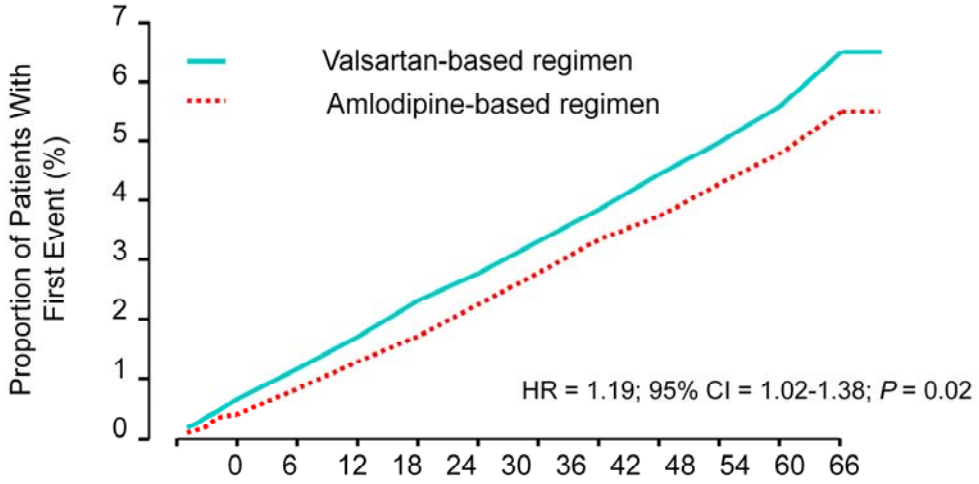
VALUE: Fatal and Non-fatal Stroke



Number at risk												
Valsartan	7649	7494	7448	7312	7170	7022	6877	6692	6515	6093	3859	1516
Amlodipine	7596	7499	7455	7334	7195	7055	6918	6744	6587	6163	3846	1532

Julius S et al. *Lancet*. June 2004;363:2022–31.

VALUE: Fatal and Non-Fatal Myocardial Infarction



Number at risk												
Valsartan	7649	7499	7458	7319	7177	7016	6853	6680	6504	6078	3864	1520
Amlodipine	7596	7497	7458	7332	7205	7065	6905	6727	6562	6141	3840	1532

Julius S et al. *Lancet*. June 2004;363:2022–31.

ARB CV outcome studies in hypertensive patients with BP reduction

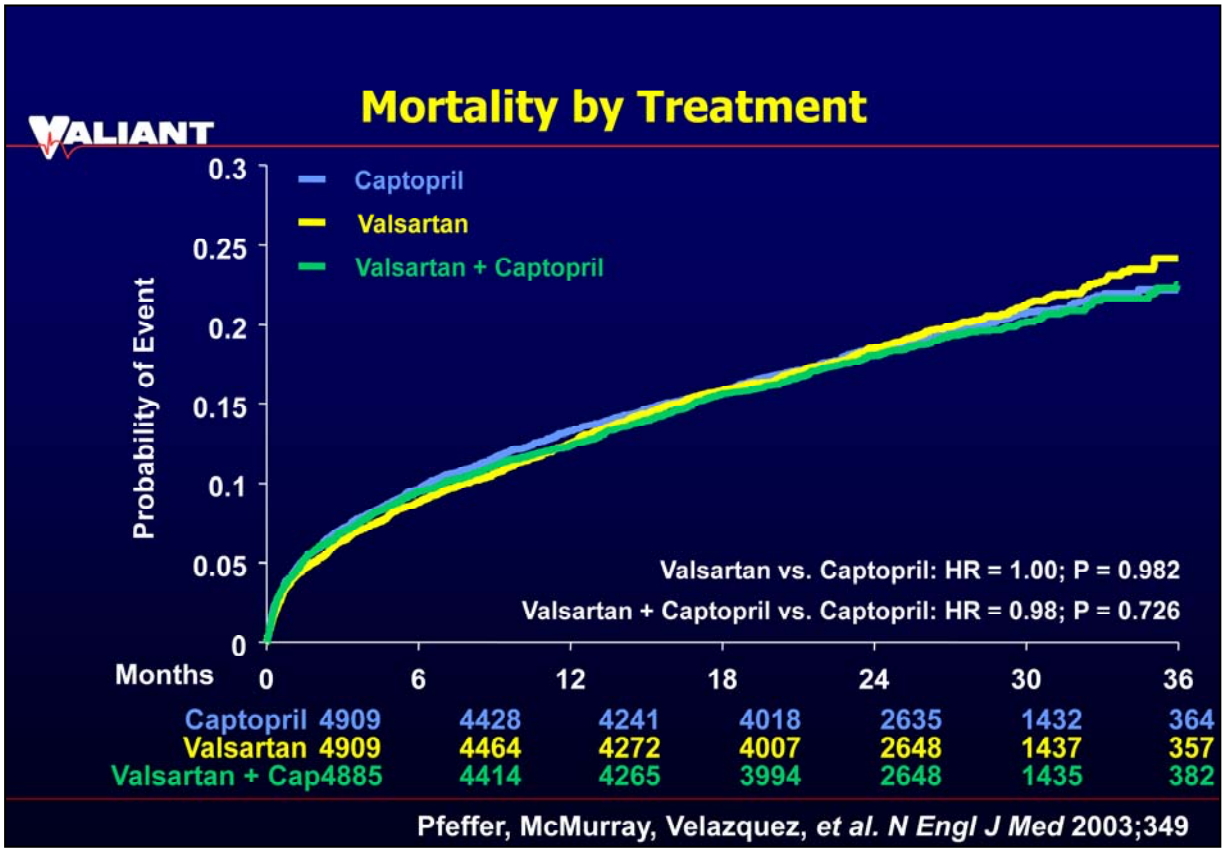
LIFE

- Losartan reduced incidence of stroke compared with atenolol in patients with severe hypertension and LVH[1]
- However, the result cannot be interpreted as the BP independent CV protection effect of Losartan (Mean baseline SBP 174.4mmHg, fell by 30.2/16.6 and 29.1/16.8 in the Losartan and Atenolol group)

VALUE

- Valsartan was not better than amlodipine in reducing CV risk in patients with hypertension and risk factors[3]
- Valsartan was significantly worse than amlodipine on the incidence of MI

1. Dahlöf B et al. Lancet 2002; 359:995-1003
2. Carlberg et al. Lancet 2004;364:1684–9
3. Julius S, et al. Lancet. 2004;363:2022-31

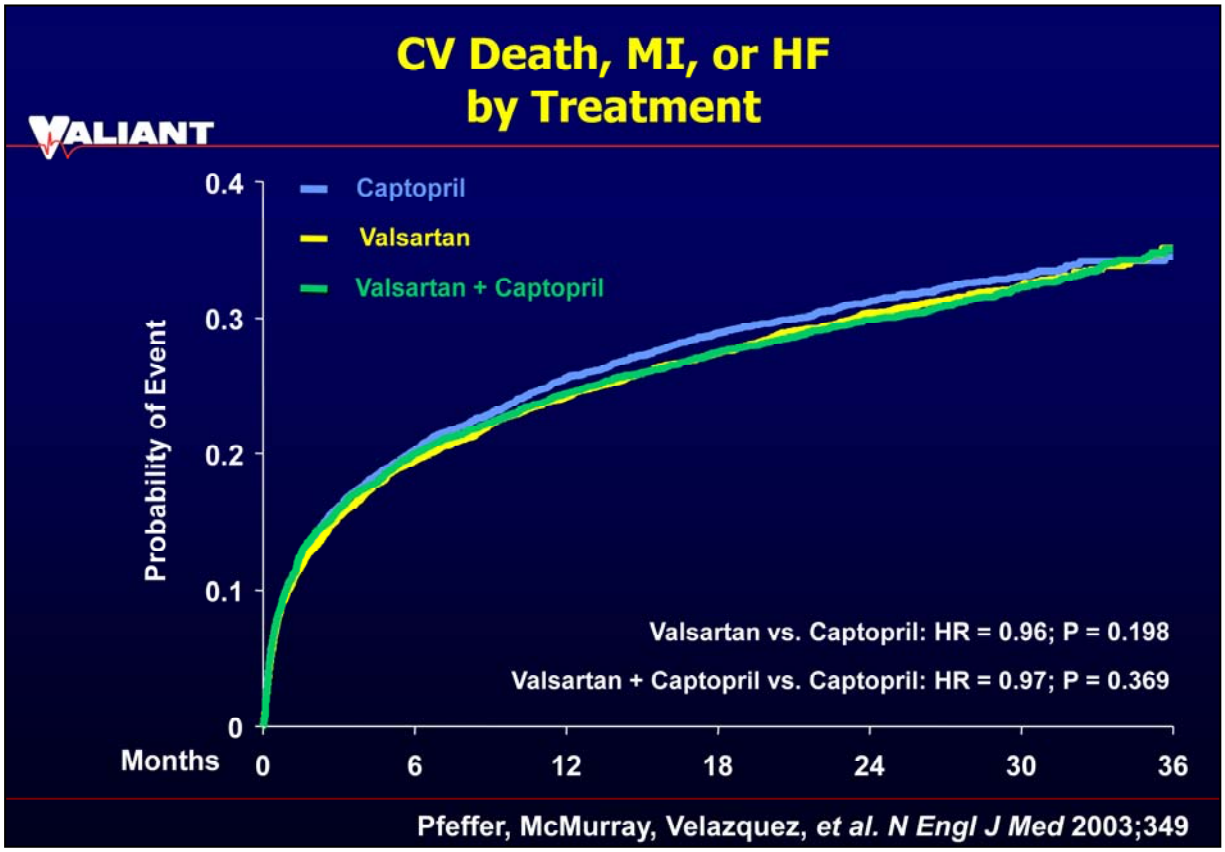


In this active-controlled, randomized trial, the mortality of the captopril group served as the comparator.

Those randomized to the valsartan arm experienced a very similar incidence of death of any cause, with a hazard ratio of 1.00.

Patients randomized to the combination of valsartan plus captopril also had a very similar incidence of death, with a hazard ratio of 0.98. Neither group being significantly different from the captopril event rate.

Pfeffer, et al., NEJM 2003;349:1893-1906



Since ACE inhibitors have been shown to reduce the risk of heart failure admissions and nonfatal MIs, as well as death, we compared the hazard ratios for this composite event of the valsartan groups to the proven captopril regimen. The event rate for the valsartan monotherapy group was similar to captopril with a hazard ratio of 0.96. The combination of valsartan plus captopril was also no different than captopril alone with a hazard ratio of 0.97.

Pfeffer, et al., NEJM 2003;349:1893-1906

CHARM Programme

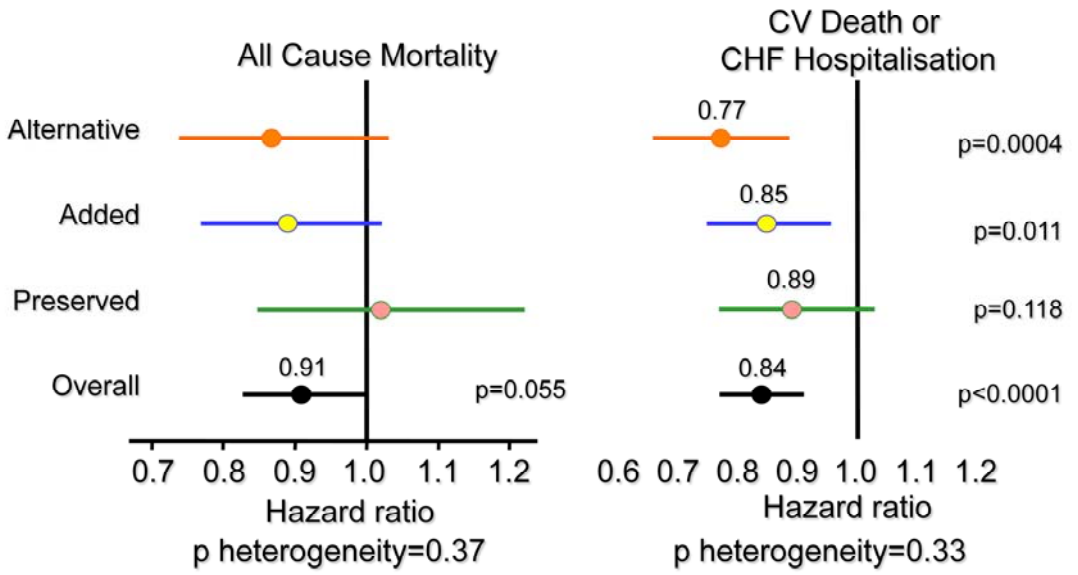
3 component trials

Patient with chronic heart failure (n=7,601), Median follow up 37.7 months
Treatment : Canderartan 32mg or placebo

Primary outcome for each trial: CV death or CHF hospitalisation

Pfeffer et al, Lancet 2003

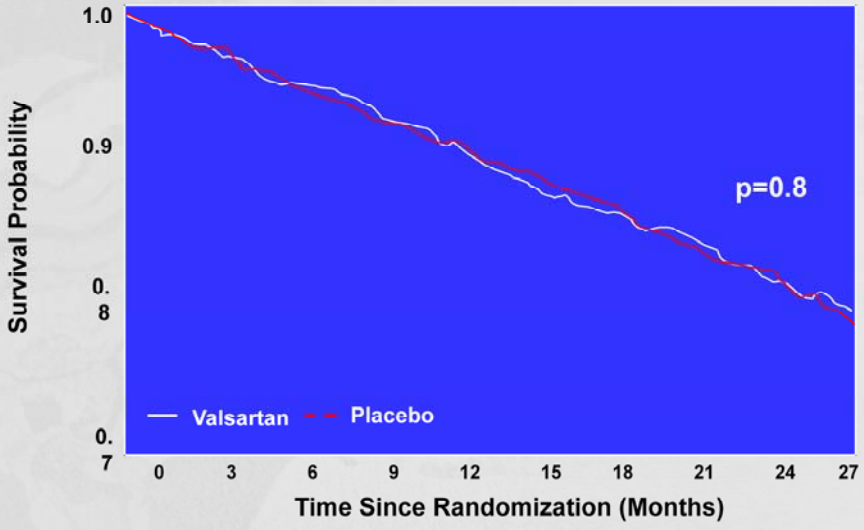
Candesartan effective in CHF patients intolerant of ACE inhibitors and only in LVEF ≤40%



Pfeffer MA, et al. Lancet 2003; 362: 759-66

Val-HeFT Results

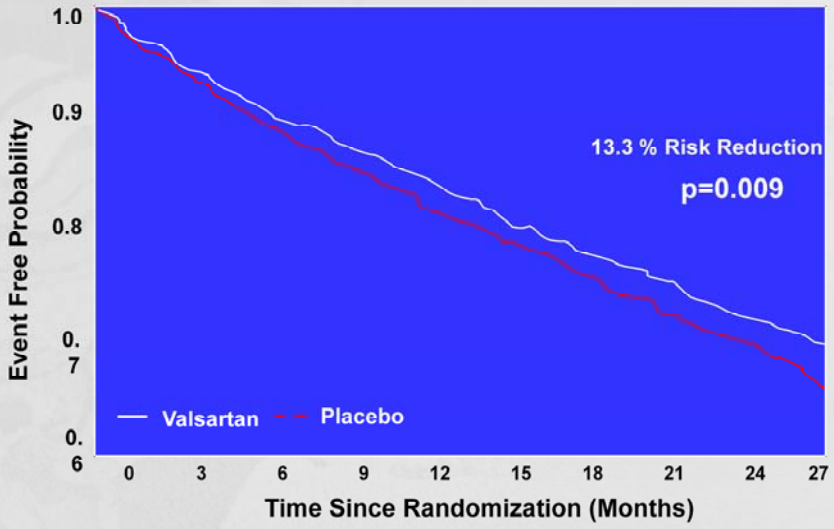
Primary Endpoint: All Cause Mortality



Val-HeFT Results

Primary Endpoint: Combined All Cause Mortality and Morbidity

5,010 Patients with heart failure of NYHA class II, III or IV
mean follow –up 23 month



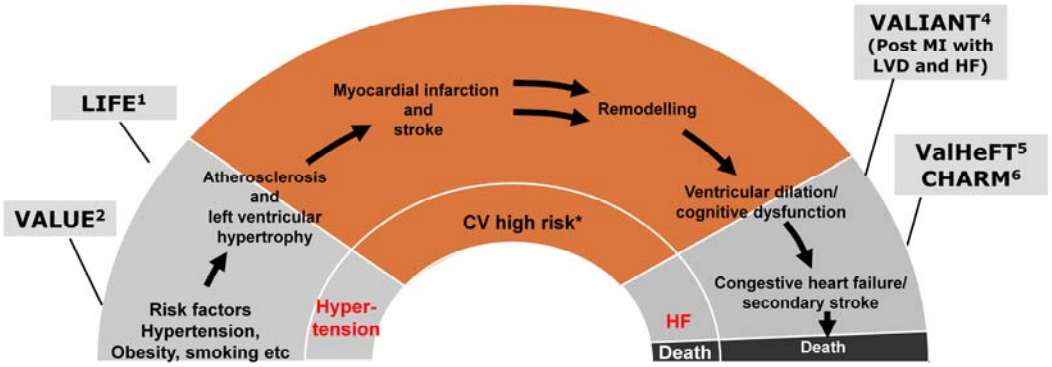
ARB CV outcome studies demonstrate effectiveness in heart failure

- Three key ARB trials have shown the effectiveness of ARBs in patients with heart failure
  - *Val-HeFT and VALIANT showed that valsartan is effective in patients with heart failure or patients with heart failure/LV dysfunction after a recent MI*, respectively*
  - *CHARM showed candesartan is also effective in heart failure*
  - *CHARM PRESERVE didn't show chadesartan is effective in LVEF> 40%*

* VALIANT (VALsartan In Acute myocardial iNfarction Trial) was conducted in clinically stable patients with symptomatic heart failure or asymptomatic left ventricular systolic dysfunction after a recent (12 hours – 10 days) myocardial infarction.

1. Pfeffer MA, et al. N Engl J Med 2003;349:1893-906; 2. Cohn JN, et al. N Engl J Med 2003;345;1667-75; 3. Pfeffer MA, et al. Lancet 2003 362: 759–66;

Before ONTARGET, ARB trials had not addressed CV high-risk patients in the middle of the CV continuum*



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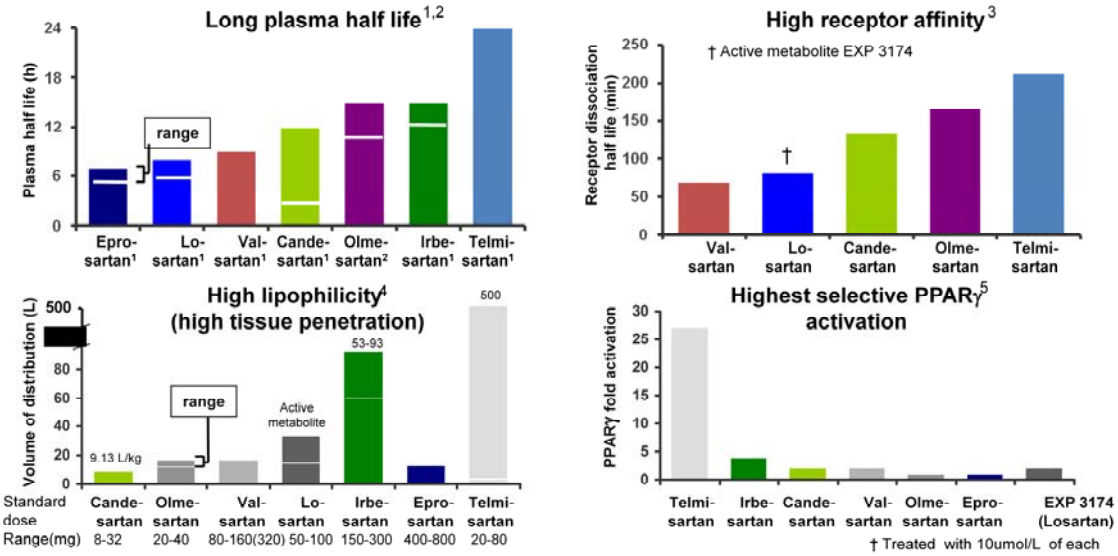
1.Lancet 2002;23:995-1003, 2. Lancet 2004;363:2022-31, 3. N Engl J Med 2008;358:1547-59, 4. N Engl J Med 2003;349:1893-906, 5.N Engl J Med 2001;345:1667, 6. Lancet 2003;362:759-66

Which ARB to reduce events in CV high-risk patients?

- Before ONTARGET, no ARB had been tested for protective effects in CV high-risk patients in middle of CV continnum
- To demonstrate effectiveness equal to the gold-standard ramipril, an ARB with the optimal pharmacology was selected
- Telmisartan has a unique pharmacology among ARBs
- This can be translates to meaningful clinical benefit over other ARBs

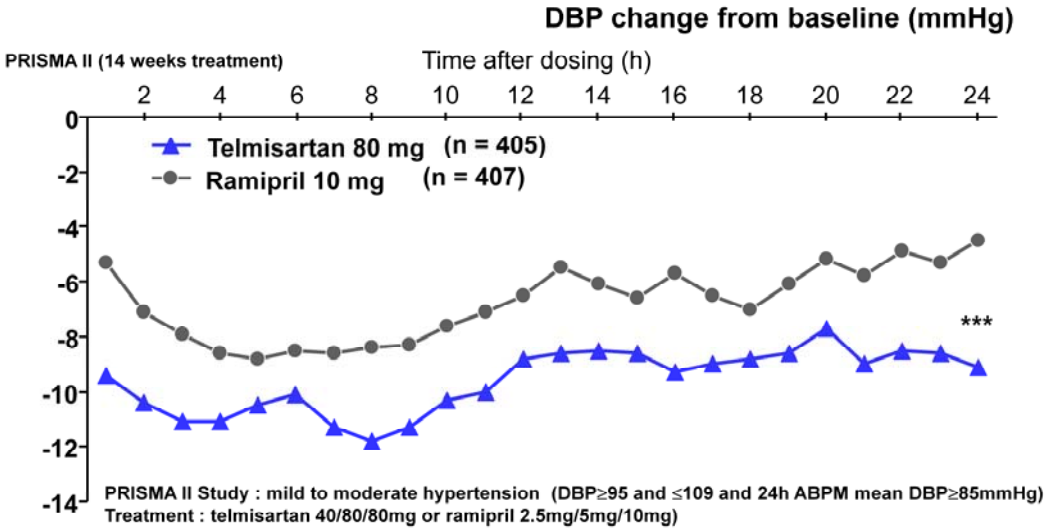
Telmisartan's unique pharmacology among ARBs

Long half life, High receptor affinity, High tissue penetration and selective PPARγ activation



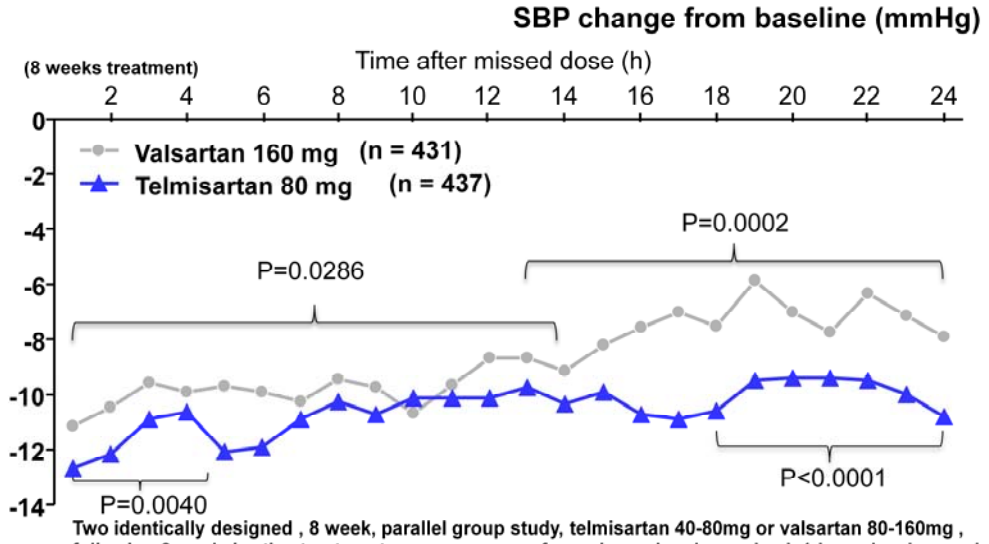
1.Burnier M. & Brunner H.R., Lancet 2000;355:637–645, 2.Brunner H.R., J Hum Hypertens 2002;16(Suppl 2):S13–S16;, 3.akuta H., *et al.* Int J Clin Pharmacol Res 2005;25:41–46, 4. Asmar,R., Int J Clin Pract. 2006;60:315-320, 5. Benson S.C. *et al.* Hypertension 2004;43:993–1002

Telmisartan is superior to ramipril in 24 hour ABPM reduction



Lacourcière et al. Am J Hypertens 2006; 19:104–112

Telmisartan is superior to Valsartan in 24 hour ABPM reduction after missed dose

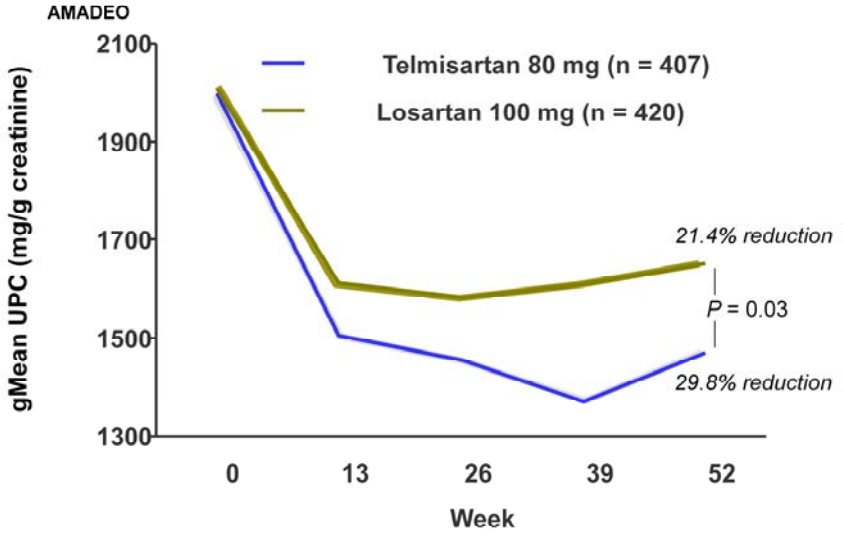


Two identically designed , 8 week, parallel group study, telmisartan 40-80mg or valsartan 80-160mg , following 2 weeks' active treatment, a cross-over performed: previously received 1days placebo received active therapy and vice versa

P values are for Telmisartan vs Valsartan comparison

Lacourcière et al. Blood Press Monit 2004:9;203–210

Telmisartan's unique pharmacology possibly translates to meaningful clinical benefit



In hypertensive diabetic nephro-pathy patients:

<DBP reduction)
Telmisartan 80 mg
DBP -3.3 mmHg
Losartan 100 mg
DBP- 2.9 mm Hg)
P=0.61

n=860

UPC : Urinary Protein –to-Creatinine

Bakris et al. Kidney Int 2008; DOI:10.1038/ki.2008.204

ONTARGET trial –

To prove BP independent CVD risk reduction in CV high-risk patients

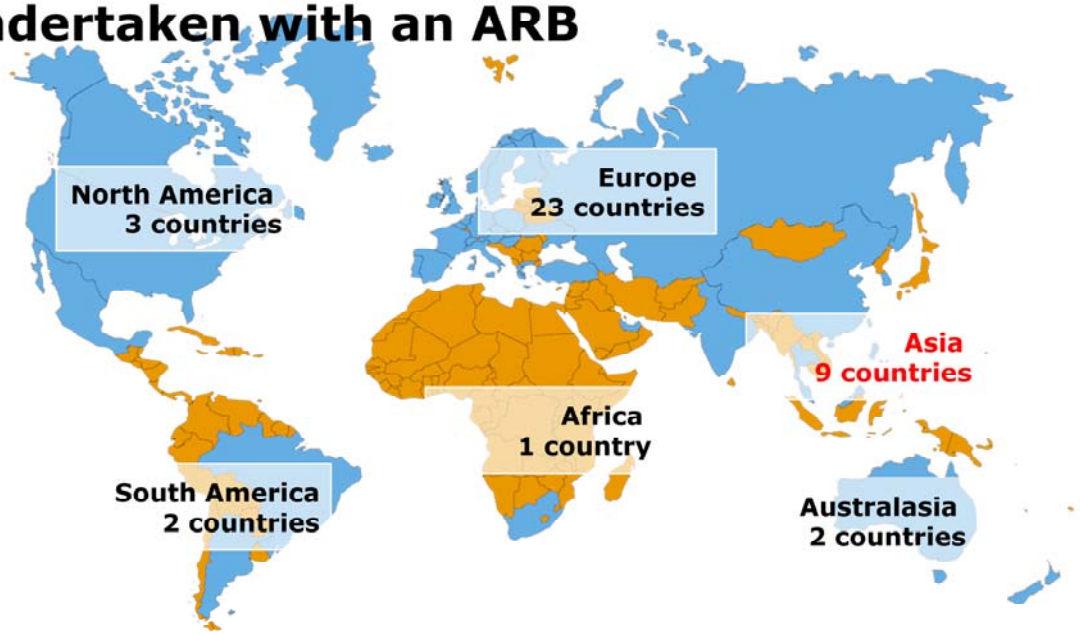
The ONTARGET® Trial Programme: study objectives

- To compare the efficacy of telmisartan with ramipril in preventing CV morbidity and mortality
- To determine any additional benefit in combining telmisartan with ramipril, compared with ramipril monotherapy (dual RAS blockade)
- In patients who are intolerant to an ACE inhibitor, the parallel TRANSCEND trial compares the efficacy of telmisartan and placebo in addition to standard therapy in preventing cardiovascular morbidity and mortality

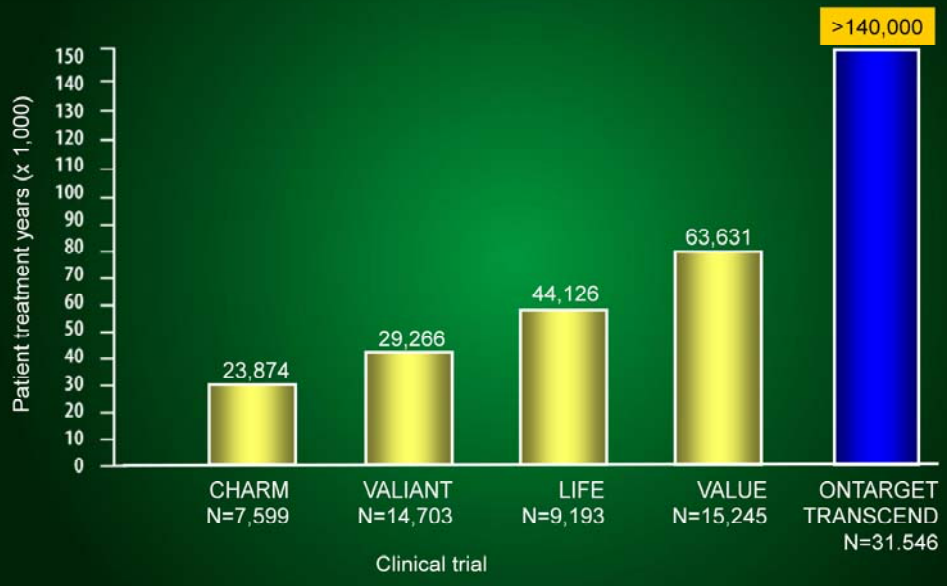
ACE = angiotensin-converting enzyme; CV = cardiovascular; RAS = renin angiotensin system; TRANSCEND = Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease

Teo K, et al. Am Heart J 2004;148:52–61; The ONTARGET Investigators. N Engl J Med 2008;358:1547–1559

The ONTARGET® Trial Programme: Largest CV protection trial ever undertaken with an ARB



ONTARGET: The largest ARB outcome trial



Collaborative Study Group, N Engl J Med 2001;345:851–860; Pfeffer M.A., N Engl J Med 2003;349:1893–1906; Swedberg K., J Card Fail 1999;5:276–282; Dahlöf B., Lancet 2002;359:995–1005; Mann J., Blood Press 1998;7:176–183; Unger T., Am J Cardiol 2003; 91 (suppl 1):28G–34G

Key inclusion and exclusion criteria

Inclusion criteria

- ***Age ≥55 years***
- ***High risk of a CVD event + a history of:***
  - *Coronary artery disease, peripheral arterial occlusive disease (PAD), cerebrovascular event, or diabetes mellitus with end-organ damage*
- ***Intolerance to ACE inhibitors (TRANSCEND only)***

Exclusion criteria

- ***Cardiovascular disease***
  - *Including symptomatic congestive heart failure or uncontrolled hypertension on treatment*
- ***Significant renal disease***
  - *Including creatinine clearance <0.6 mL/s or serum creatinine >265 µmol/L, documented significant renal artery stenosis, or proteinuria (for TRANSCEND only)*
- ***Hepatic dysfunction***
  - *Including SGPT (ALT) or SGOT (AST) >4x upper limit of normal (ULN), additional criteria for hepatic impairment, total bilirubin >20 µmol/L, or biliary obstructive disorders*

CVD = cardiovascular disease; TRANSCEND = Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease; SGPT = serum glutamic pyruvic transaminase; ALT = alanine aminotransferase; SGOT = serum glutamic oxaloacetic transaminase; ALT = aspartate aminotransferase

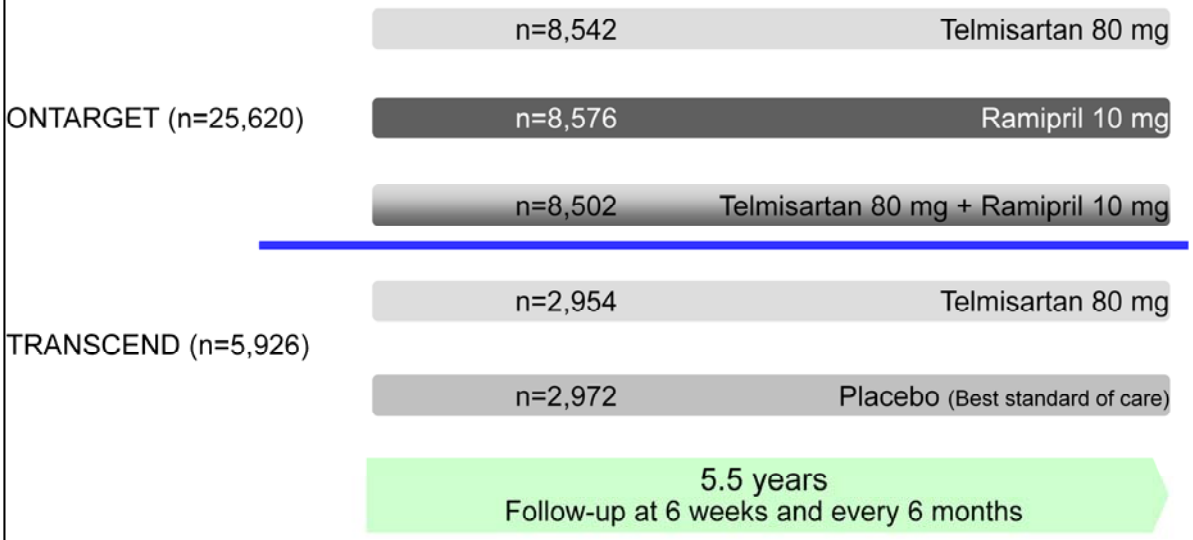
Teo K, et al. Am Heart J 2004;148:52–61; The ONTARGET Investigators. N Engl J Med 2008;358:1547–1559

Study endpoints

Primary endpoints	***Composite CV endpoint***
	Cardiovascular mortality
	Non-fatal myocardial infarction
	Hospitalisation for congestive heart failure
	Non-fatal stroke
Secondary endpoints	***Newly diagnosed congestive heart failure***
	Cardiovascular revascularisation procedure
	Newly diagnosed diabetes
	Cognitive decline
	New onset of atrial fibrillation
	Nephropathy
Other endpoints	***Non-cardiovascular death, total mortality***
	Unstable, new and worsening angina
	Transient ischaemic attack
	Microvascular complications of diabetes (laser therapy for diabetic retinopathy)
	Non-fatal malignancy

CV = cardiovascular
Teo K, et al. Am Heart J 2004;148:52–61; The ONTARGET Investigators. N Engl J Med 2008;358:1547–1559

The ONTARGET® Trial Programme in CV high-risk Patients – The largest ARB outcomes trial



* In patients intolerant of ACEIs

Teo K, et al. Am Heart J 2004;148:52–61; The ONTARGET Investigators. N Engl J Med 2008;358:1547–1559;
The TRANSCEND Investigators. Lancet 2008; 372:1174-83.

ONTARGET – like HOPE – is not a hypertension trial

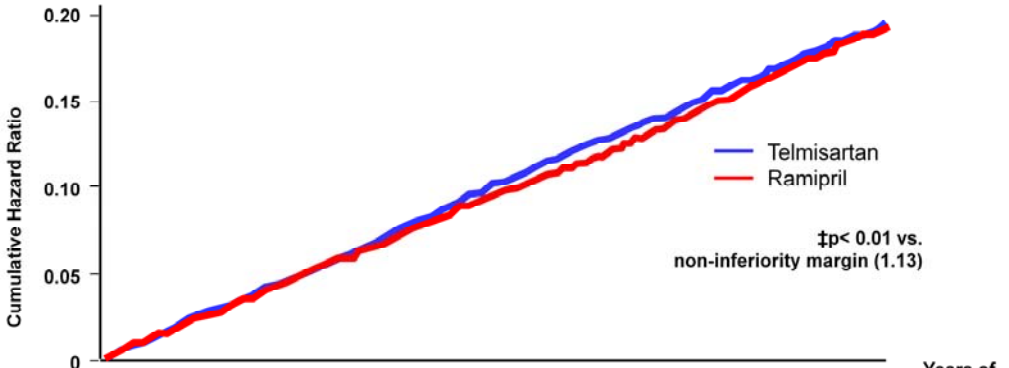
	ONTARGET® (n=25,620)	HOPE (n=9,541)
Age (years)	66.4	65.9
Male (%)	73.3	73.3
BP at entry (mm Hg)	143/82	139/79
Medical history (%)		
Myocardial infarction	*48.7*	*52.8*
Stable angina	*34.8*	*55.8*
Stroke/transient ischaemic attack	*20.7*	*10.8*
Peripheral Arterial Disease	*11.8*	*15.9*
Diabetes	*37.3*	*38.3*
Concomitant medications (%)		
Beta-blockers	56.9	39.5
Diuretics	27.9	15.1
Statins	60.7	28.9

† n=9538; ‡ n=9297.

Sleight P. Acta Diabetol 2005;42:S50–56; Teo K, et al. Am Heart J 2004;148:52–61; Yusuf S, et al. N Engl J Med 2000;342:145–153.

Telmisartan 80mg reduces devastating CV events similar to ramipril 10mg in CV high-risk patients

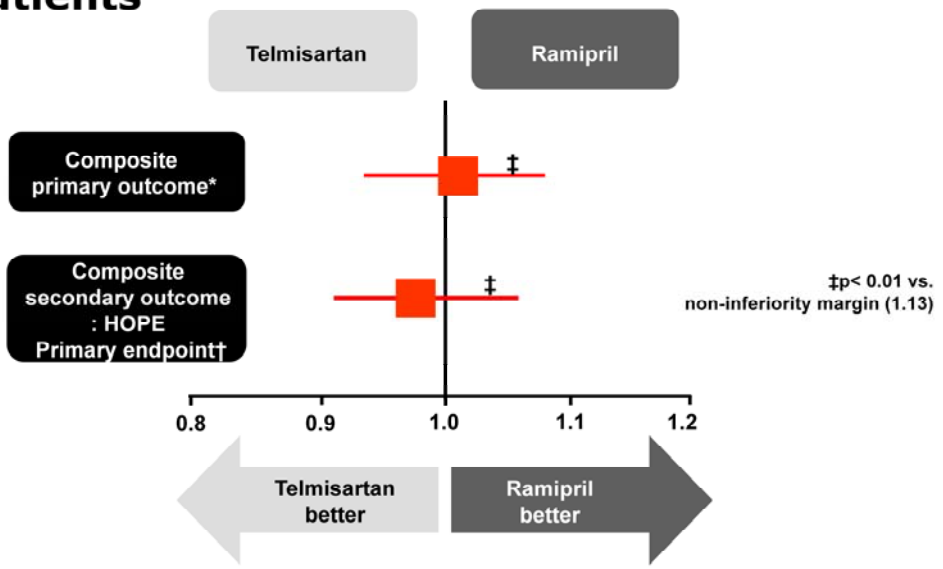
Reduction in composite CV risk*



No. at risk	0	1	2	3	4	5
Telmisartan	8,452	8,177	7,778	7,420	7,051	1,687
Ramipril	8,576	8,214	7,832	7,472	7,093	1,703

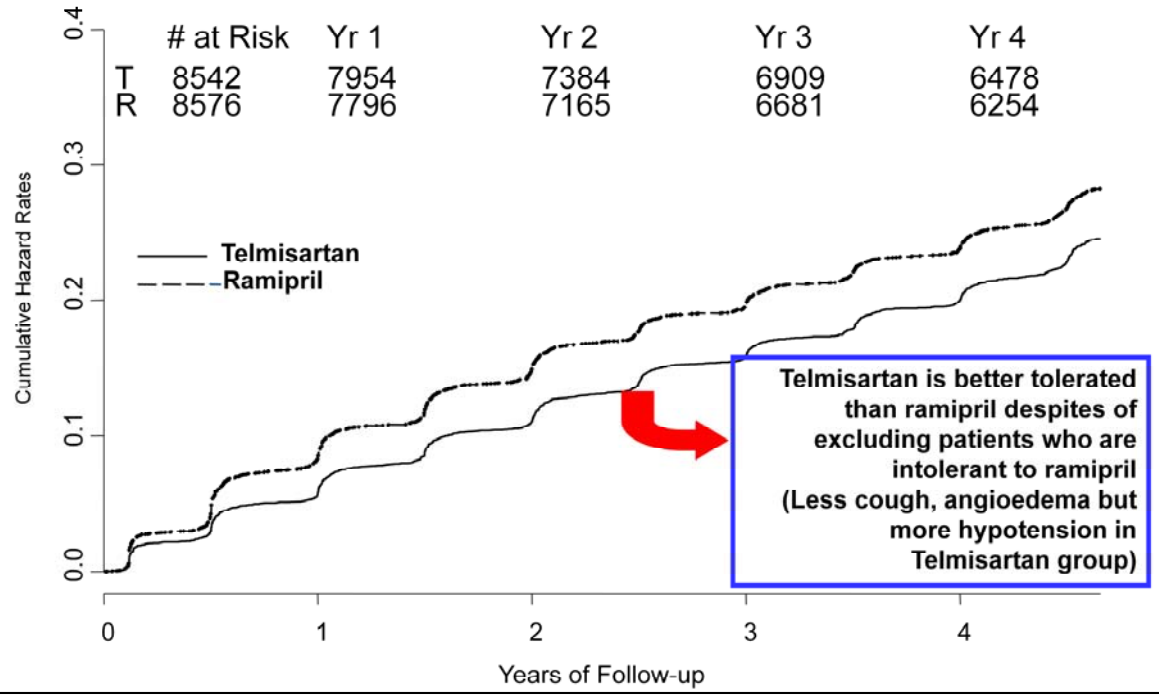
* Reduction in composite CV risk (Primary endpoint: cardiovascular mortality, non-fatal myocardial infarction, hospitalisation for congestive heart failure, non-fatal stroke)
The ONTARGET Investigators. N Engl J Med 2008;358:1547–1559

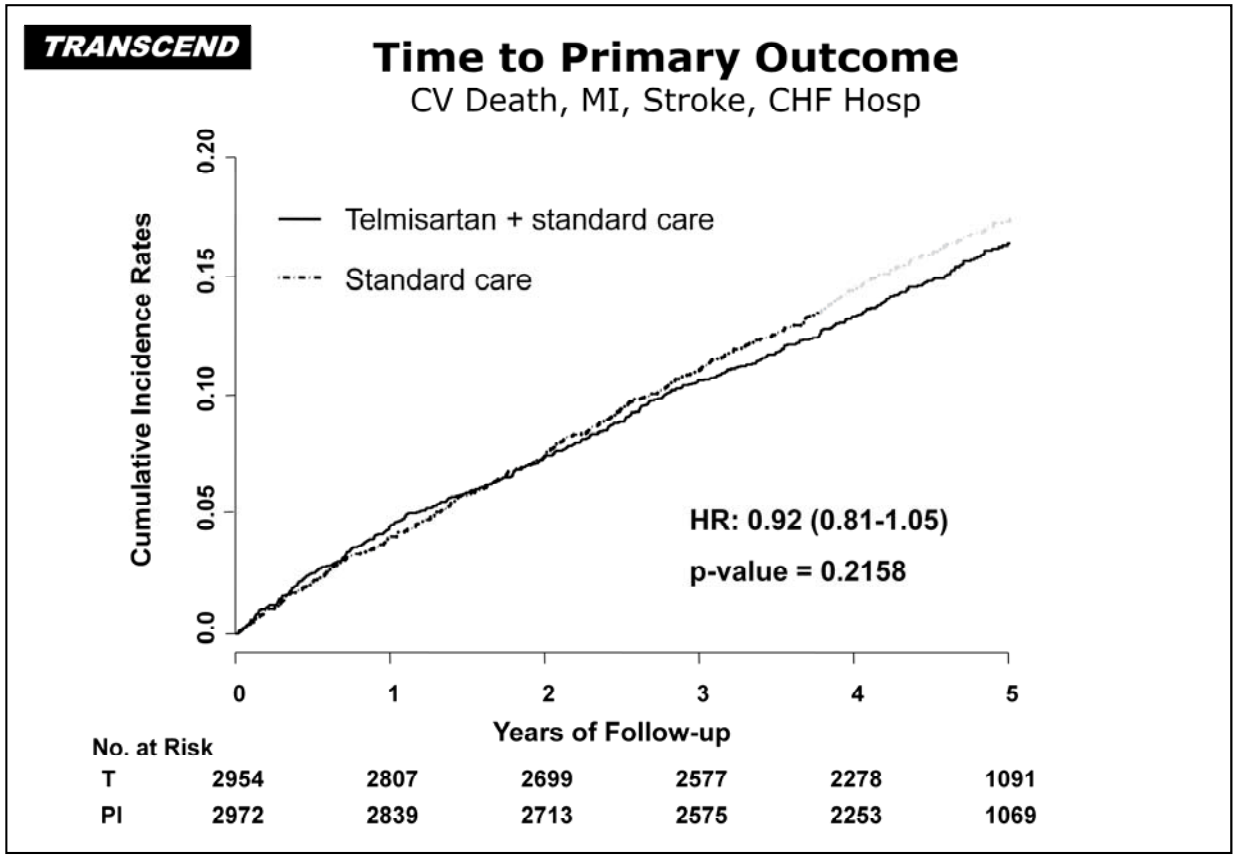
Telmisartan 80mg reduces devastating CV events similar to ramipril 10mg in CV high-risk patients

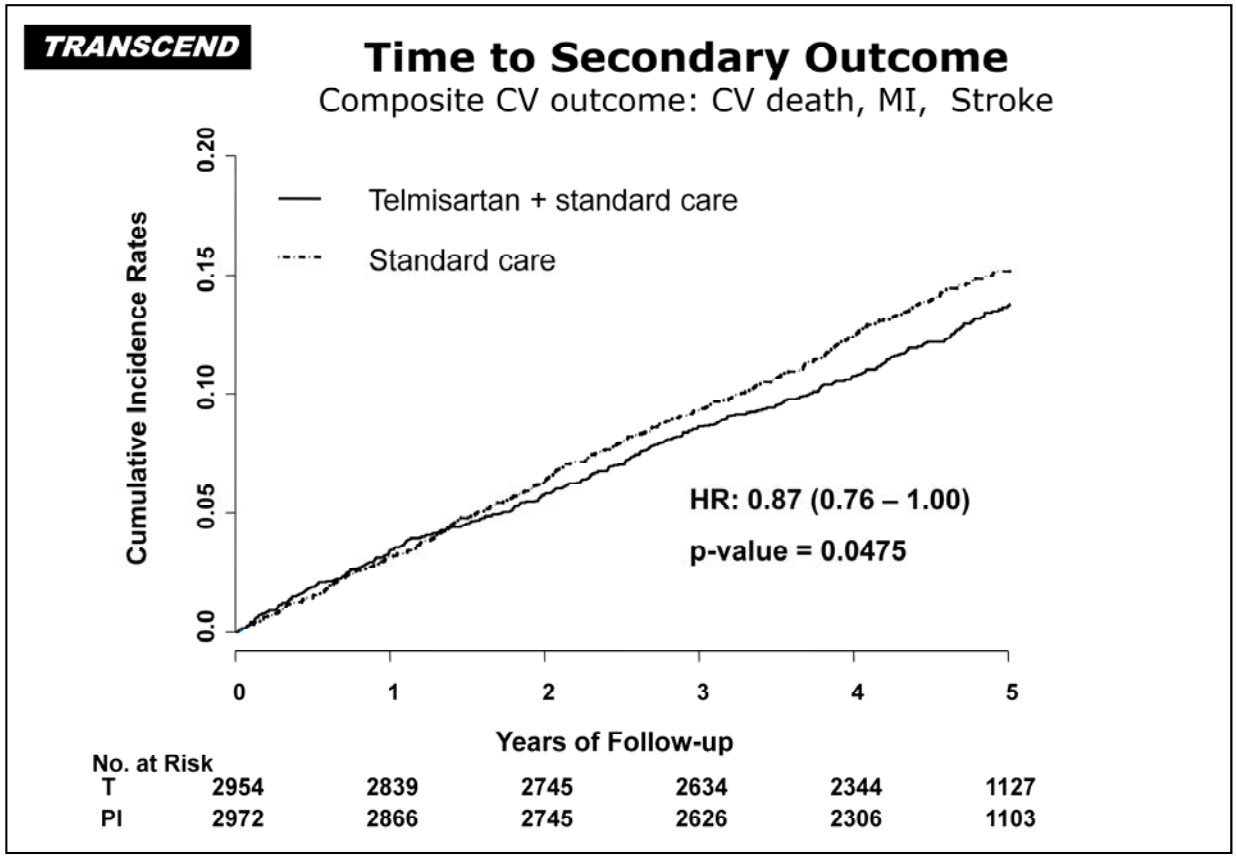


* ONTARGET primary composite outcome = CV death + MI + stroke+ hospitalization for CHF
† HOPE primary endpoint = CV death + MI + stroke
The ONTARGET Investigators. N Engl J Med 2008;358:1547–1559

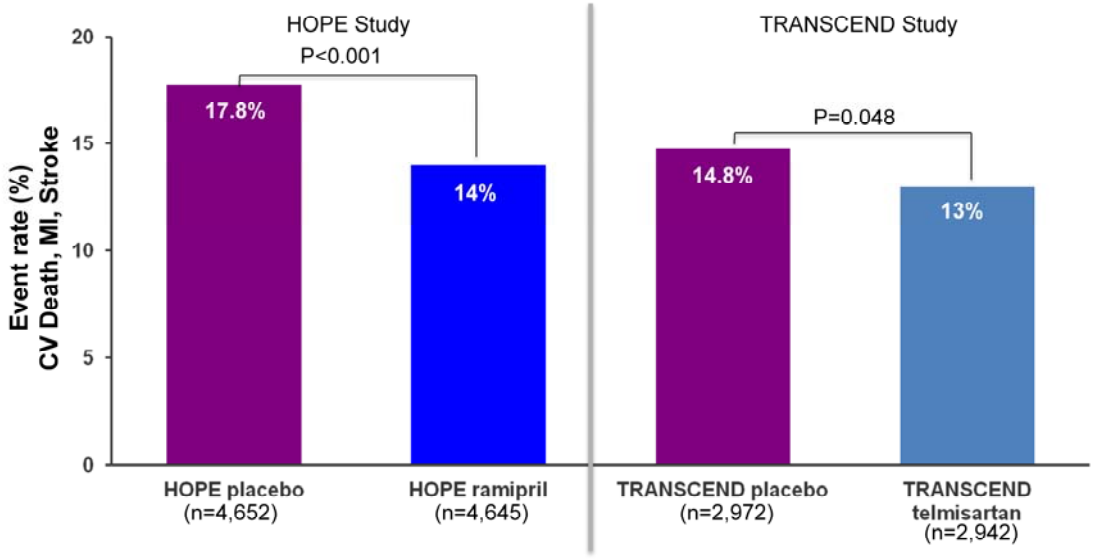
ONTARGET Time to Permanent Discontinuation of Study Medication




TRANSCEND
Time to Primary Outcome
CV Death, MI, Stroke, CHF Hosp
Cumulative Incidence Rates
0.0
0.05
0.10
0.15
0.20
Telmisartan + standard care
Standard care
HR: 0.92 (0.81-1.05)
p-value = 0.2158
0
1
2
3
4
5
Years of Follow-up
No. at Risk
T 2954 2807 2699 2577 2278 1091
Pl 2972 2839 2713 2575 2253 1069


TRANSCEND
Time to Secondary Outcome
Composite CV outcome: CV death, MI, Stroke
Telmisartan + standard care
Standard care
Cumulative Incidence Rates
0.0
0.05
0.10
0.15
0.20
HR: 0.87 (0.76 – 1.00)
p-value = 0.0475
0
1
2
3
4
5
Years of Follow-up
No. at Risk
T 2954 2839 2745 2634 2344 1127
Pl 2972 2866 2745 2626 2306 1103

CV event protection in HOPE and TRANSCEND



The TRANSCEND Investigators. Lancet 2008;372:1174–1183
Yusuf S, et al. N Engl J Med 2000; 342:145–153

Use of added BP-lowering drugs was higher in control group than telmisartan group (TRANSCEND study)

	Baseline		Final	
in %	Tel	Control	Tel`	Control
Antiplatelet agents	79.8	79.0	76.8	77.0
Beta-blockers	59.3	57.2	56.6	59.0
Diuretics	33.2	32.8	33.7	40.0*
Calcium Channel blockers	39.9	40.4	38.0	45.9*
Statins	55.7	54.7	63.8	63.1

*p<0.0001 versus telmisartan 80 mg; Tel = telmisartan + standard care; Control = standard care

The TRANSCEND Investigators. Lancet 2008;372:1174–1183

ONTARGET Trial summary

- Largest ever trial investigating the reduction of cardiovascular morbidity and mortality
- Telmisartan demonstrated long-term CV protection similar to the reference standard ACE-inhibitor, ramipril in a broad range of high-risk patients
- Results demonstrate the CV protective effects of telmisartan beyond blood pressure reduction
- Telmisartan was better tolerated than ramipril and provided greater long-term adherence, despite the fact that patients were selected for ramipril tolerance at start

Conclusions

- Angiotensin II plays a central role in CV disease progression, and RAS blockade reduces cell and tissue damage
- The HOPE study showed that ramipril reduces the risk of CV events in a broad cross-section of high-risk patients beyond BP
- ACEI therapy is limited by intolerance and non-adherence; ARBs offer RAS blockade with fewer cough and angioedema and better treatment adherence
- ARBs have been investigated in different patient populations: hypertension with risk factors, CV high-risk patients, and heart failure.
- Only Telmisartan is indicated to reduce cardiovascular morbidity in CV high-risk patients (i.e. with diabetes and target organ damage, or atherothrombotic disease) – representing the majority of the patients typically seen in clinical practice

Conclusion

Telmisartan *is*

a RAS blockade with ***proven beneficial effect***

alternative *to proven ACEIs*

in ***high risk patients***