A Fresh Look at ARBs : Focus on HF survival data

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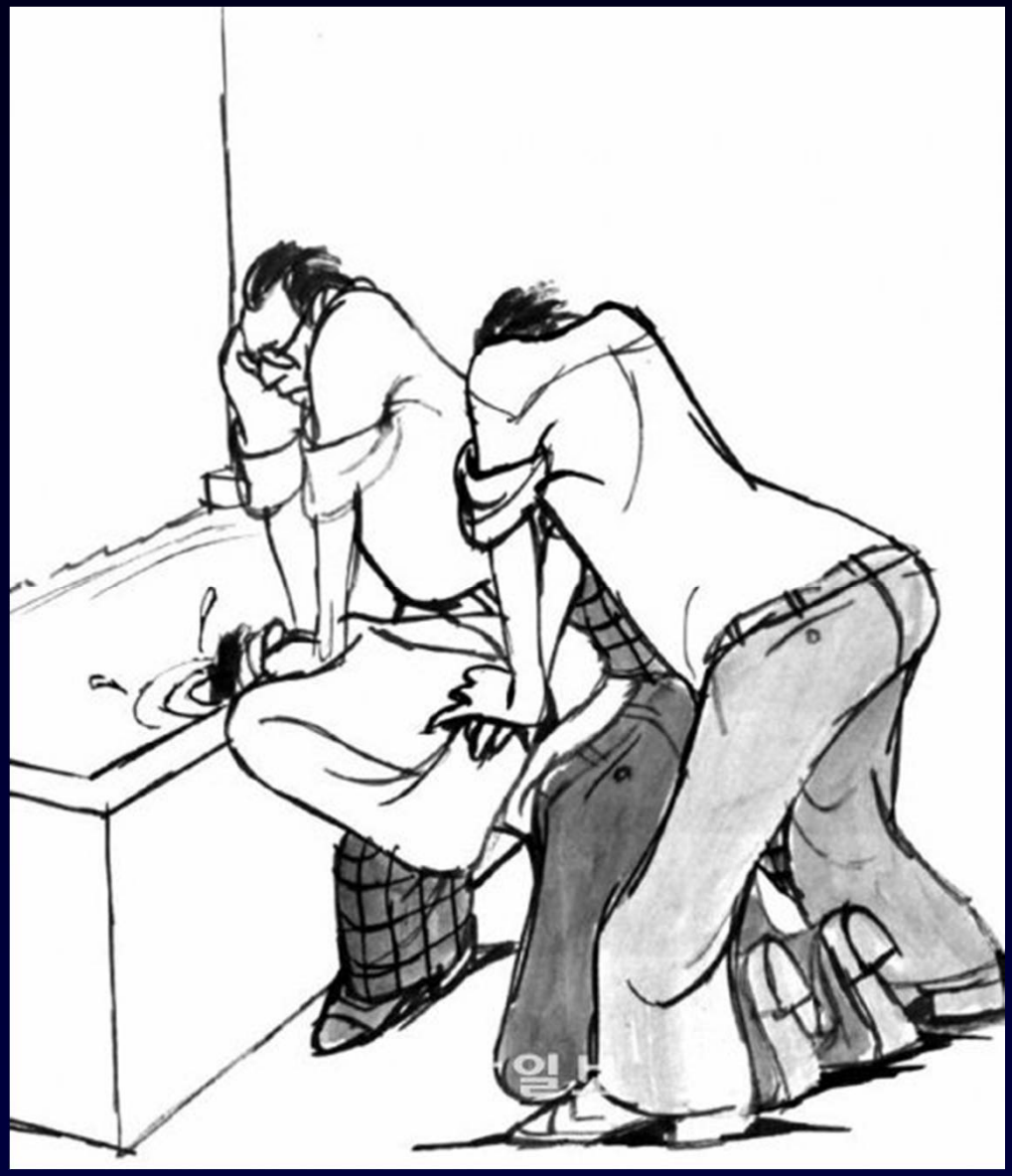
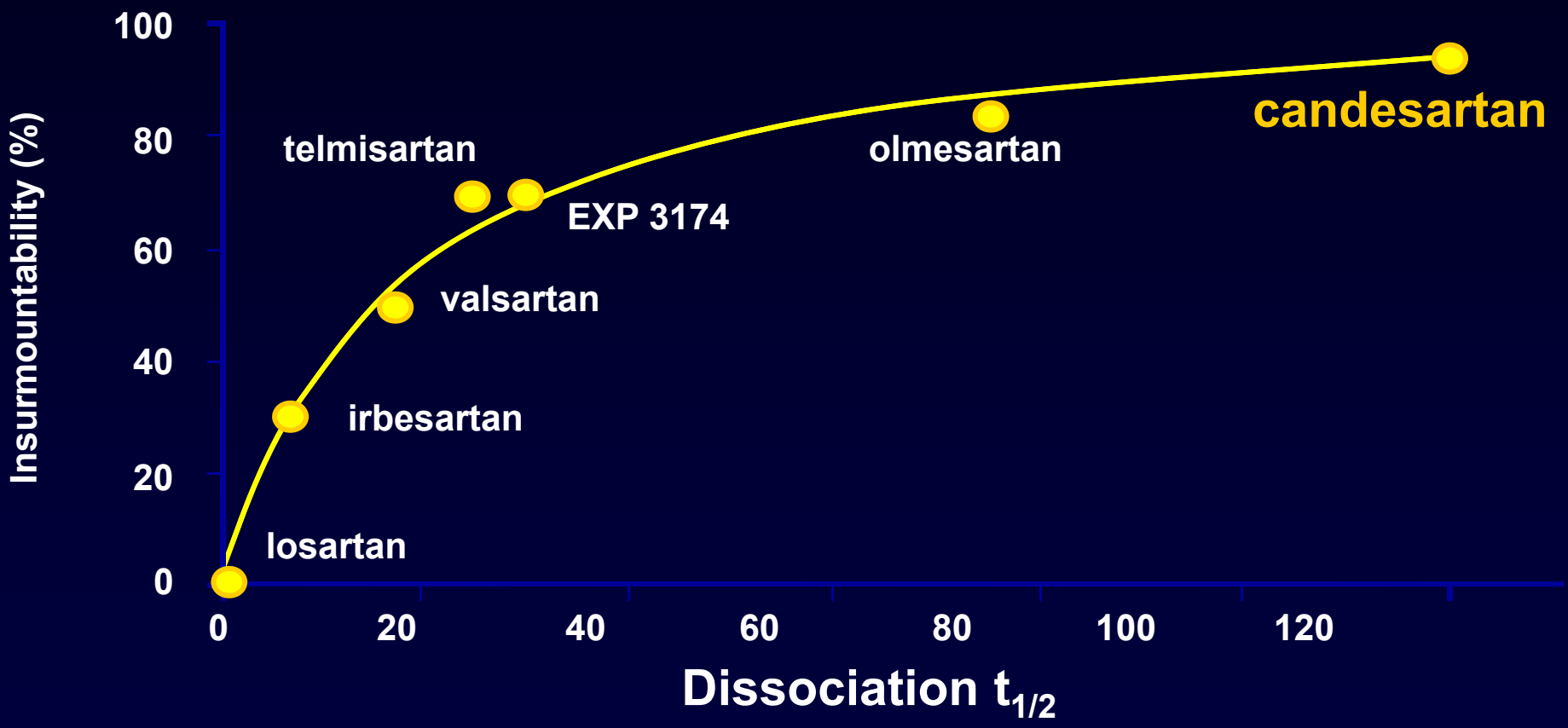
HF specialists



ARBs, are they really same?

- Pharmacodynamic : Half-life ?
- Binding affinity : Binding half-life ?
- Hydrophilicity vs. Lipophilicity ?
- Clinical study design?
- Patient type?

Binding ability to the AT1-receptor

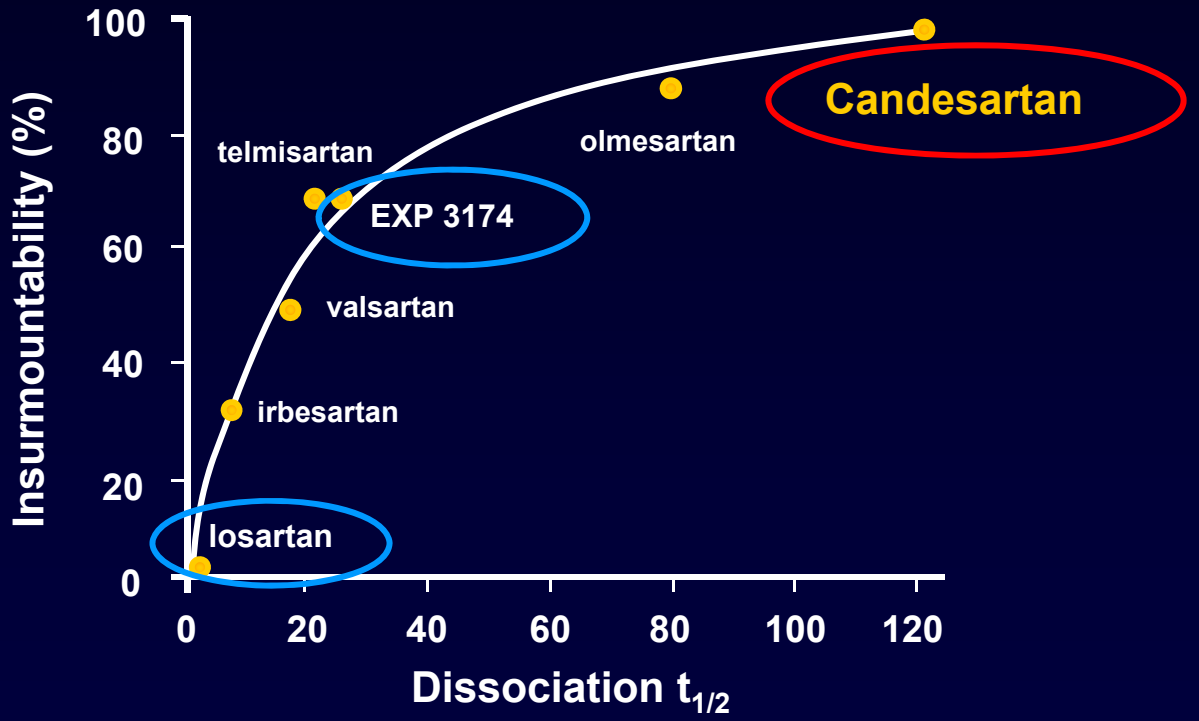


Correlation between the degree of insurmountability (I.e. the [IR*]/([IR]+[IR*]) ratio) and the corresponding experimental half-lives ($t_{1/2}$ in min) of sartan dissociation from the human AT_1 receptor stably expressed in recombinant CHO-hAT_1 cells. Data are from Table 1; $t_{1/2}$ was arbitrarily set to 1 min for losartan. The curve was drawn according to a hyperbolic function with GraphPad Prism software (GraphPad Software Inc., San Diego, CA)

Liefde and Vauquelin, Mol Cell Endocrinol 2009;302:237-43

Binding ability to the AT_1-receptor

- Candesartan and losartan have significant pharmacological differences*
  - ✓ Atacand binds harder to the AT_1-receptor
  - ✓ Atacand binds longer to the AT_1-receptor



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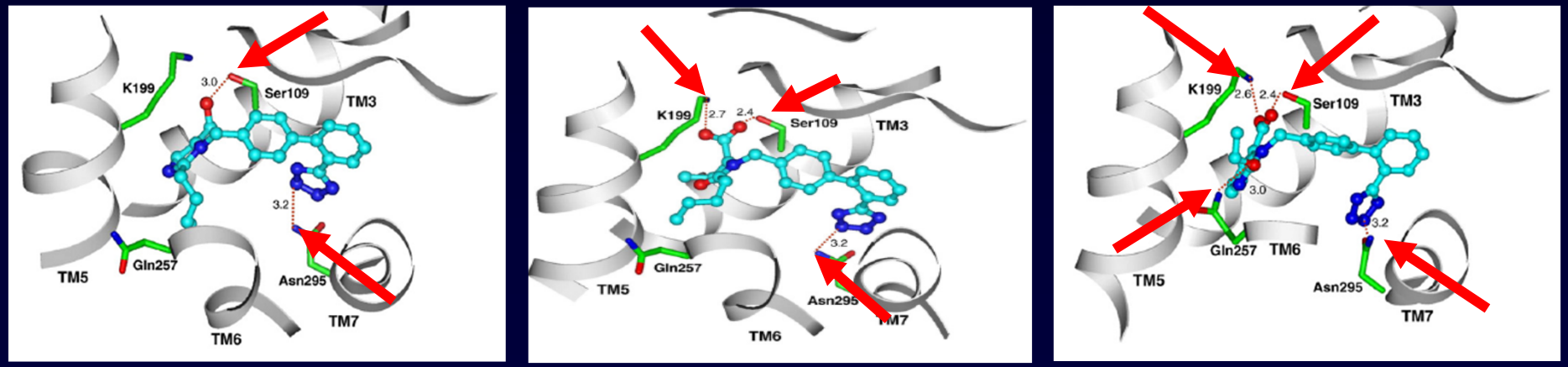
Van Liefde I, et al. Molecular and cellular endocrinology. 2009; 302 : 237–243

Number of AT_1-receptor binding sites

Candesartan compared with losartan has higher binding affinity for the AT_1 receptor, is more effective at lowering blood pressure, and is associated with less de novo HF when used in hypertension.

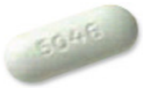
2 sites - losartan	3 sites - valsartan	4 sites - candesartan



Hydrogen bonds between ligand and receptor are shown as red dotted lines with hydrogen bond lengths. Carbon atoms of the ligands are colored light blue and those of the receptors are green

Bhuiyan MA et al. Life Sci. 2009 ;85:136-40.

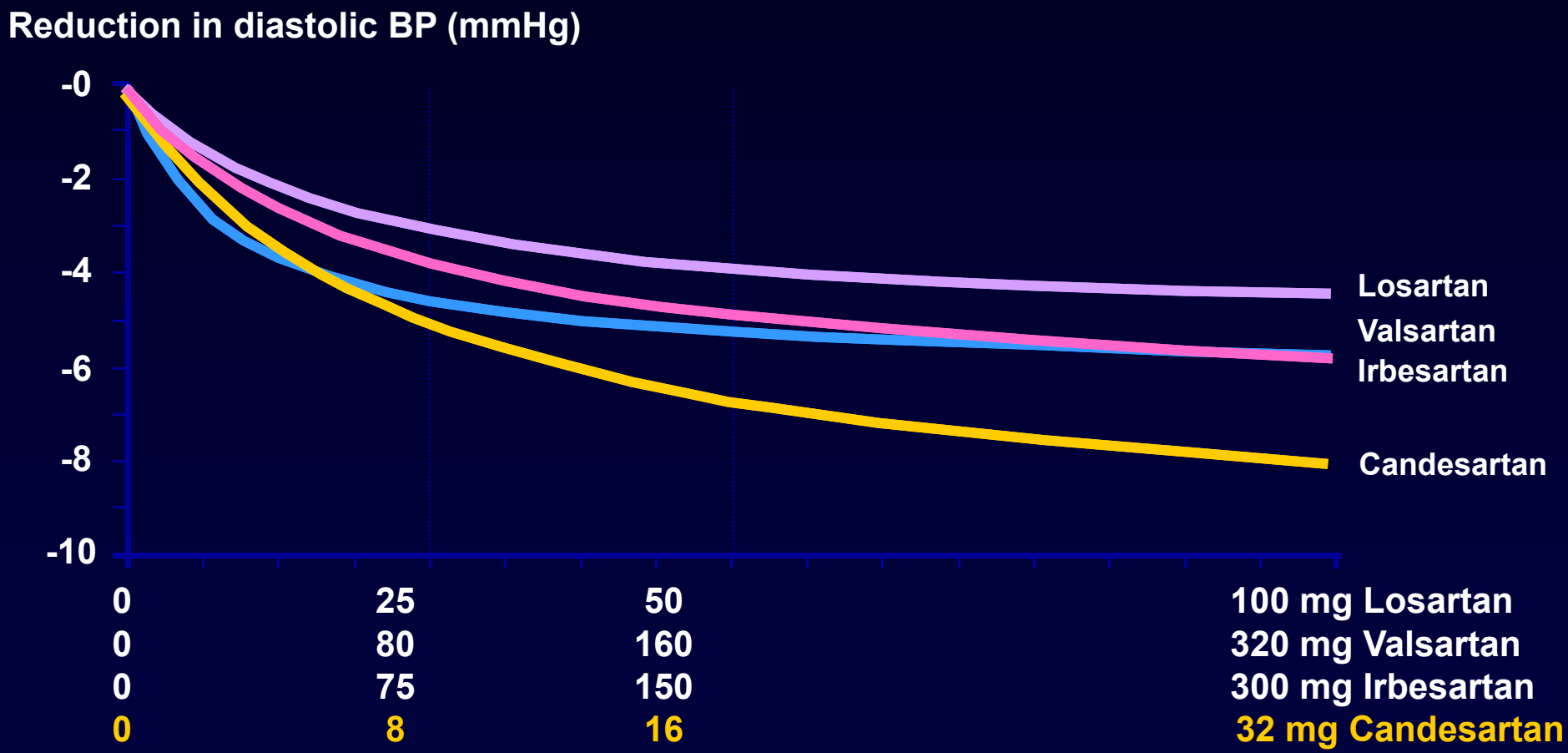
Small pill of ARBs

	Monotherapy		Combination Therapy	
Candesartan		16 mg		16/12.5
Eprosartan		600 mg		600/12.5
Irbesartan		300 mg		300/12.5
Telmisartan		80 mg		80/12.5
Losartan		100 mg		100/25
Valsartan		160 mg		160/12.5

ARBs, are they really same?

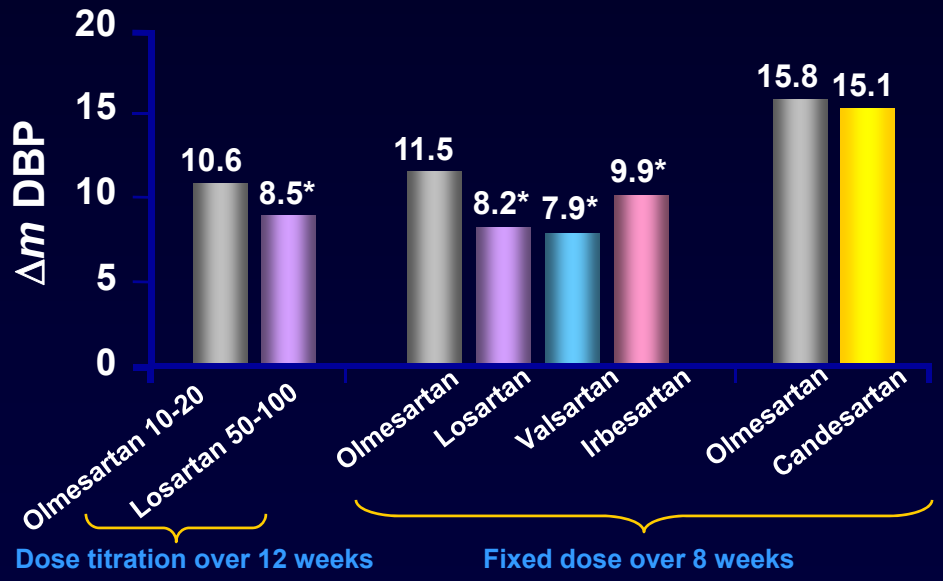
- BP control efficacy
- Beyond BP control effect in HF
  - Existence of Clinical Evidence
  - Difference in Result

Meta-analysis based on ARB new drugs application evaluation reports

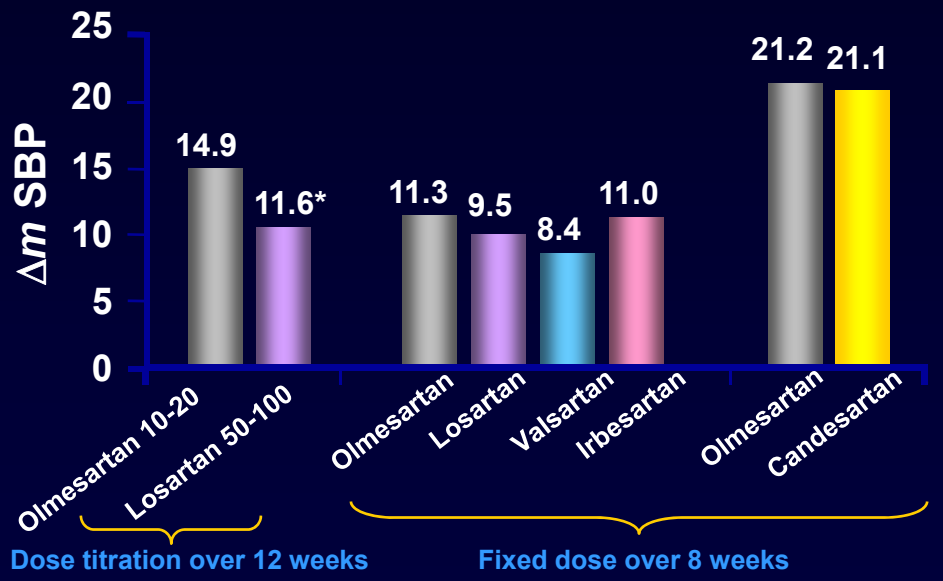


Elmfeldt et al, Blood Press. 2002;11(5):293-301.

Blood pressure-lowering efficacy of olmesartan relative to other angiotensin II receptor antagonists: an overview of randomized controlled studies



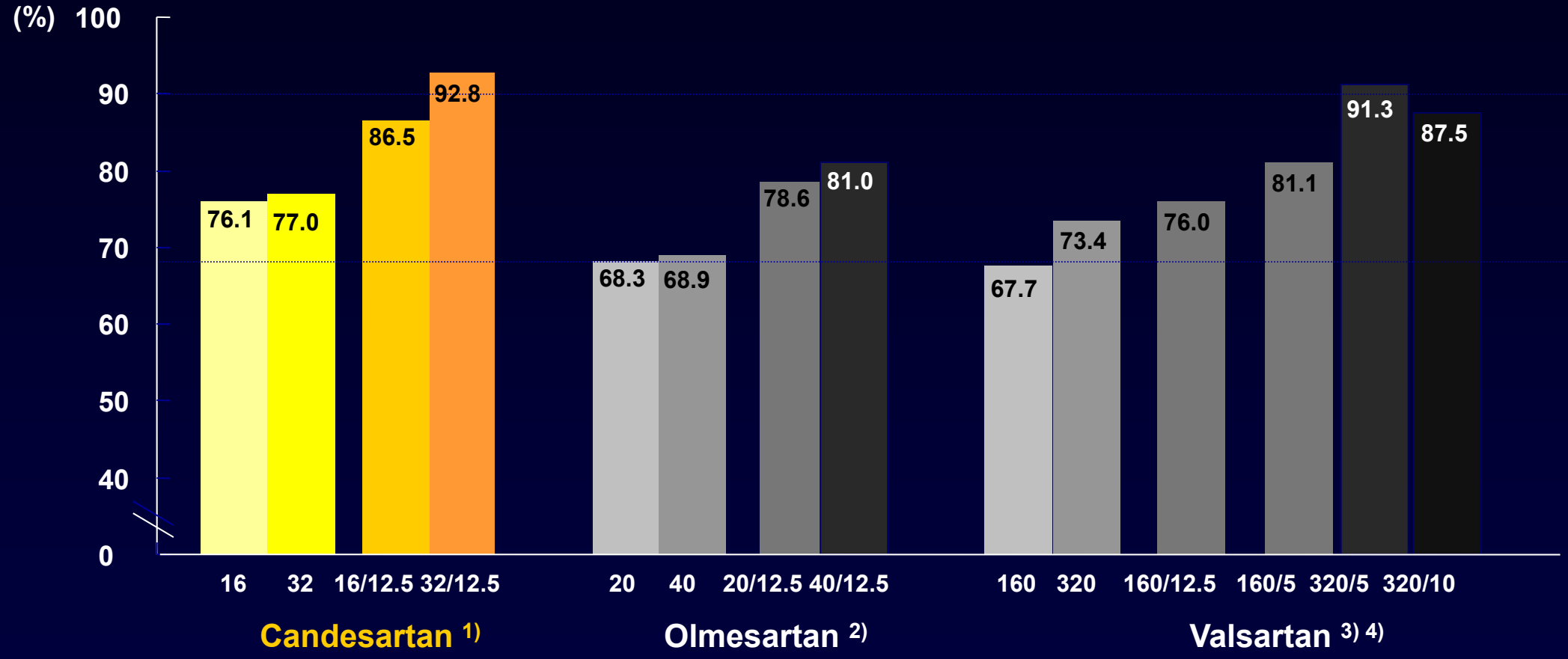
Changes from baseline in casual diastolic blood pressure In comparative studies. *p<0.05 vs. olmesartan



Changes from baseline in casual systolic blood pressure In comparative studies. *p<0.05 vs. olmesartan

Zannad and Fay. Fundam Clin Pharmacol. 2007 Apr;21(2):181-90.

Response rates from ARB studies



Responders : DBP <90 mm Hg or Decrease ≥10 mm Hg

1. CAESAR, data on file
2. Chrysant SG et al, AJH 2004;17:252-9
3. Philipp T et al, Clinical therapeutics 2007;29:1-18
4. Benz JR et al, J Hum Hypertens 1998;12:861-6

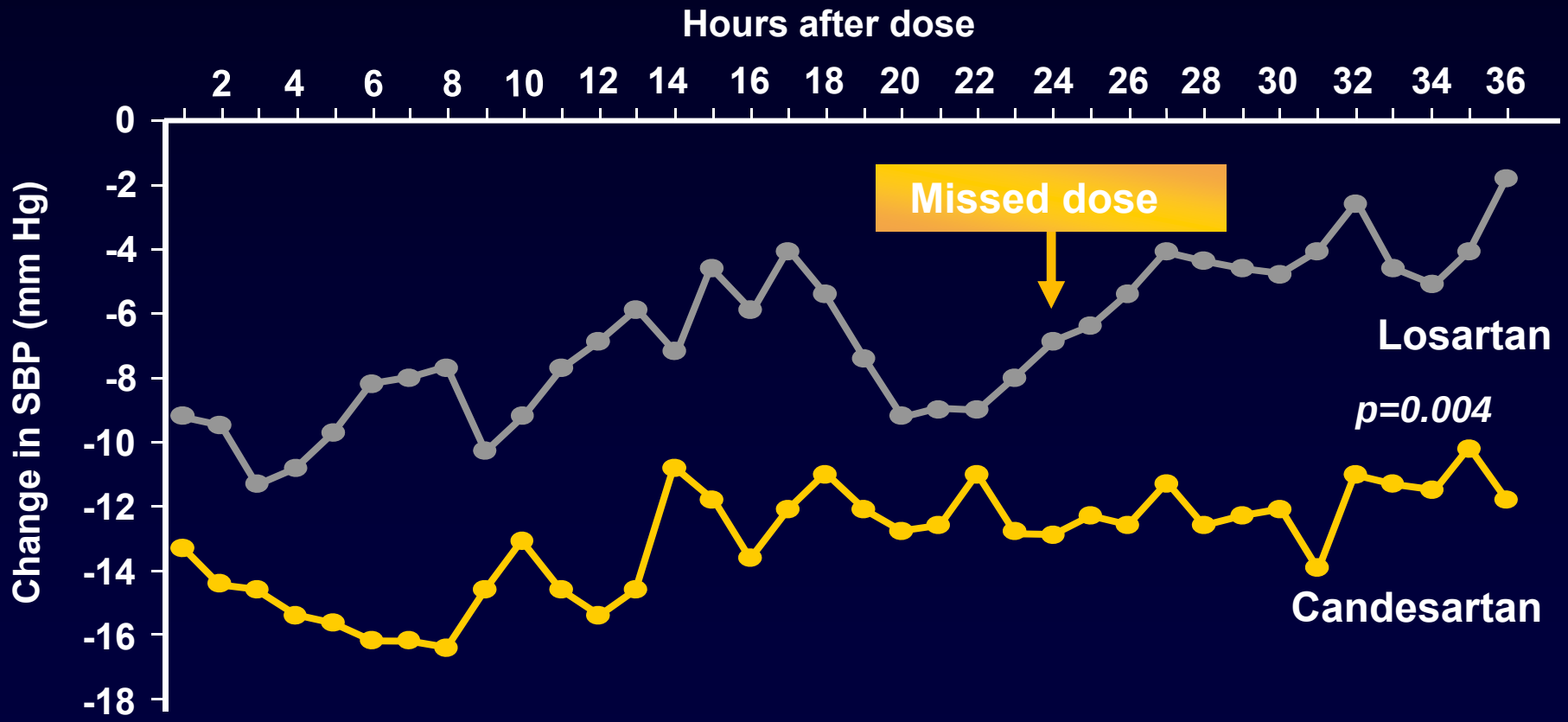
Blood pressure before and 2 years after switching from losartan to candesartan

	Before switch		2 years post-switch		p-value*	
	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
Normal (n=42)	142 ± 12.1	81 ± 6.6	133 ± 11.5	79 ± 5.5	0.0002	0.06
Diabetes (n=19)	137 ± 12.5	78 ± 5.2	128 ± 10.6	73 ± 5.7	0.007	0.00005
CVD (n=20)	132 ± 13.2	76 ± 6.3	129 ± 17.5	75 ± 10.7	0.48	0.81
All (n=81)	138 ± 12.9	79 ± 6.6	131 ± 13.1	77 ± 7.6	0.00004	0.0069

* Paired Student's *t*-test, CVD, cardiovascular disease

Usher-Smith J. Int J Clin Pract. 2008 Mar;62(3):480-4

Duration of blood pressure lowering effect 100 mg Losartan vs. 16 mg Candesartan



Lacourcière Y, et al. *Am J Hypertens* 1999; 12:1181-7

ARBs, Are they really Same?

- BP control efficacy → Different
- Beyond BP control effect
  - Existence of Clinical Evidence
  - Difference in Result

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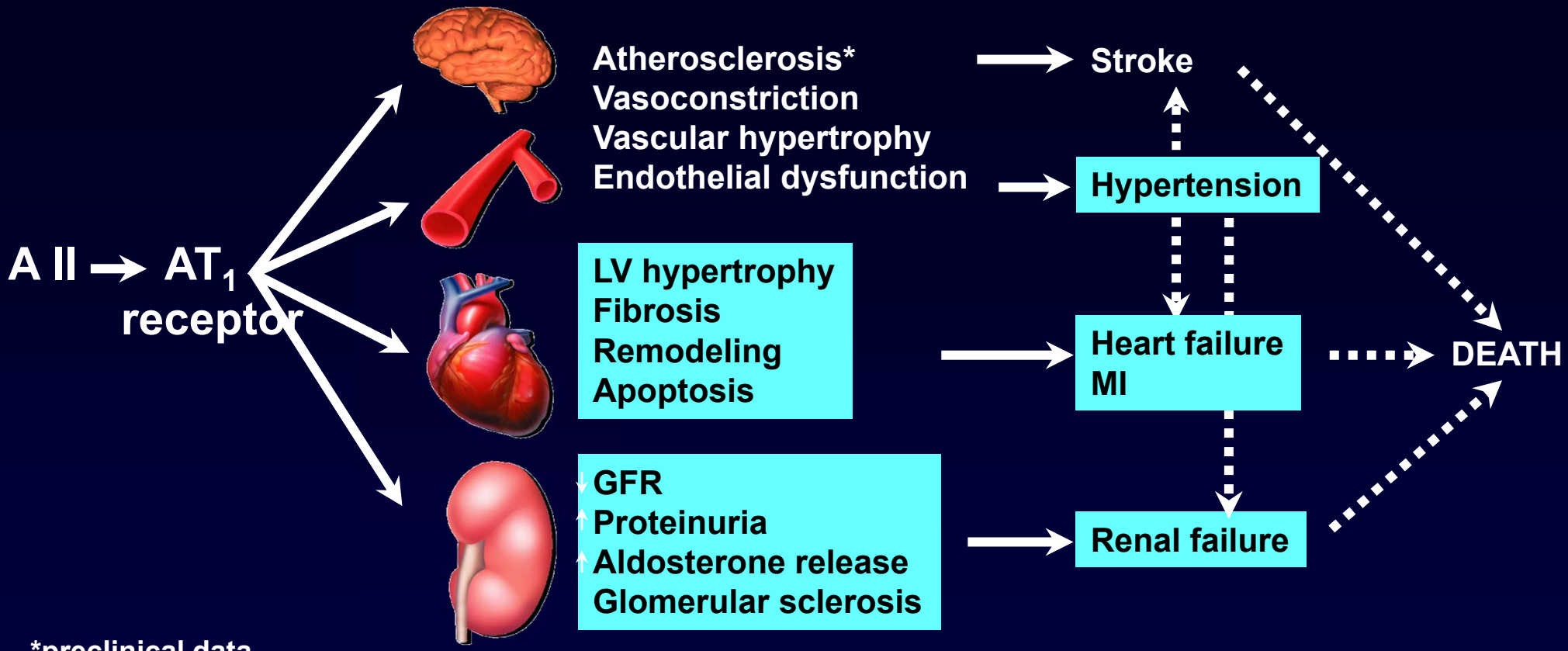
Angiotensin II Plays a Central Role in Organ Damage



*preclinical data

LV = left ventricular; MI = myocardial infarction; GFR = glomerular filtration rate

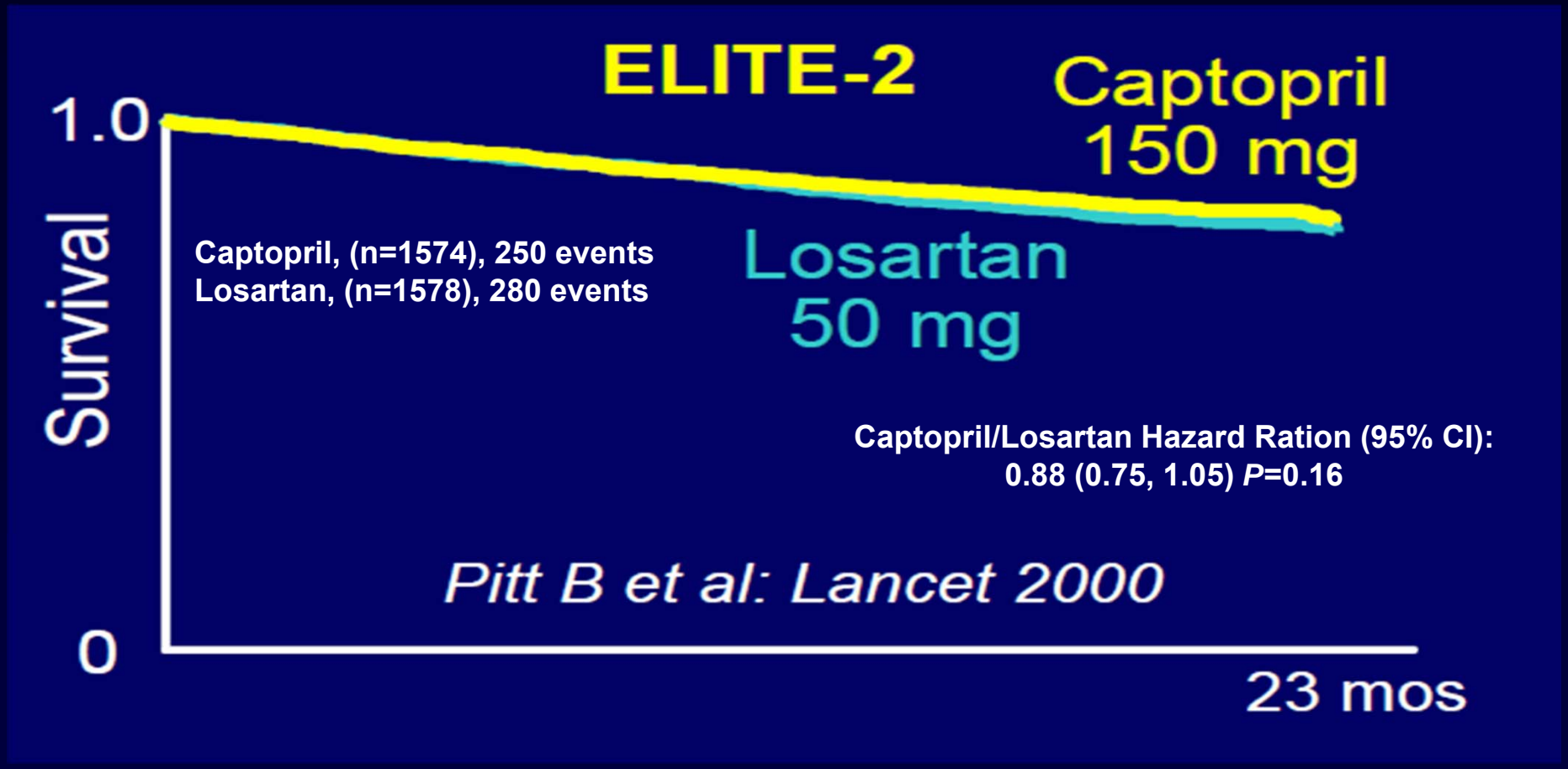
Adapted from Willenheimer R et al *Eur Heart J* 1999; 20(14): 997–1008, Dahlöf B *J Hum Hypertens* 1995; 9(suppl 5): S37–S44, Daugherty A et al *J Clin Invest* 2000; 105(11): 1605–1612, Fyhrquist F et al *J Hum Hypertens* 1995; 9(suppl 5): S19–S24, Booz GW, Baker KM *Heart Fail Rev* 1998; 3: 125–130, Beers MH, Berkow R, eds. *The Merck Manual of Diagnosis and Therapy*. 17th ed. Whitehouse Station, NJ: Merck Research Laboratories 1999: 1682–1704, Anderson S *Exp Nephrol* 1996; 4(suppl 1): 34–40, Fogo AB *Am J Kidney Dis* 2000; 35(2):179–188

Is there Clinical Studies for Target Organ Protection?

		Candesartan	Irbesartan	Losartan	Olmesartan	Telmisartan	Valsartan
Heart	CHF	O	O	O			O
	LVH	O	O	O		O	O
	AF	O	O	O			O
Brain	Stroke	O	O	O		O	O
	Dementia	O					
Kidney	Nephropathy	O	O	O		O	O
DM	Retinopathy	O					
		CHARM CASE-J SCOPE SMART DIRECT	IRMA IDNT I-PRESERVE	LIFE OPTIMAL RENAAL ELITE		ONTARGET DETAIL PROFESS	Val-Heft VALUE VALIANT ABCD-2V

ARBs in Heart Failure

All-cause mortality

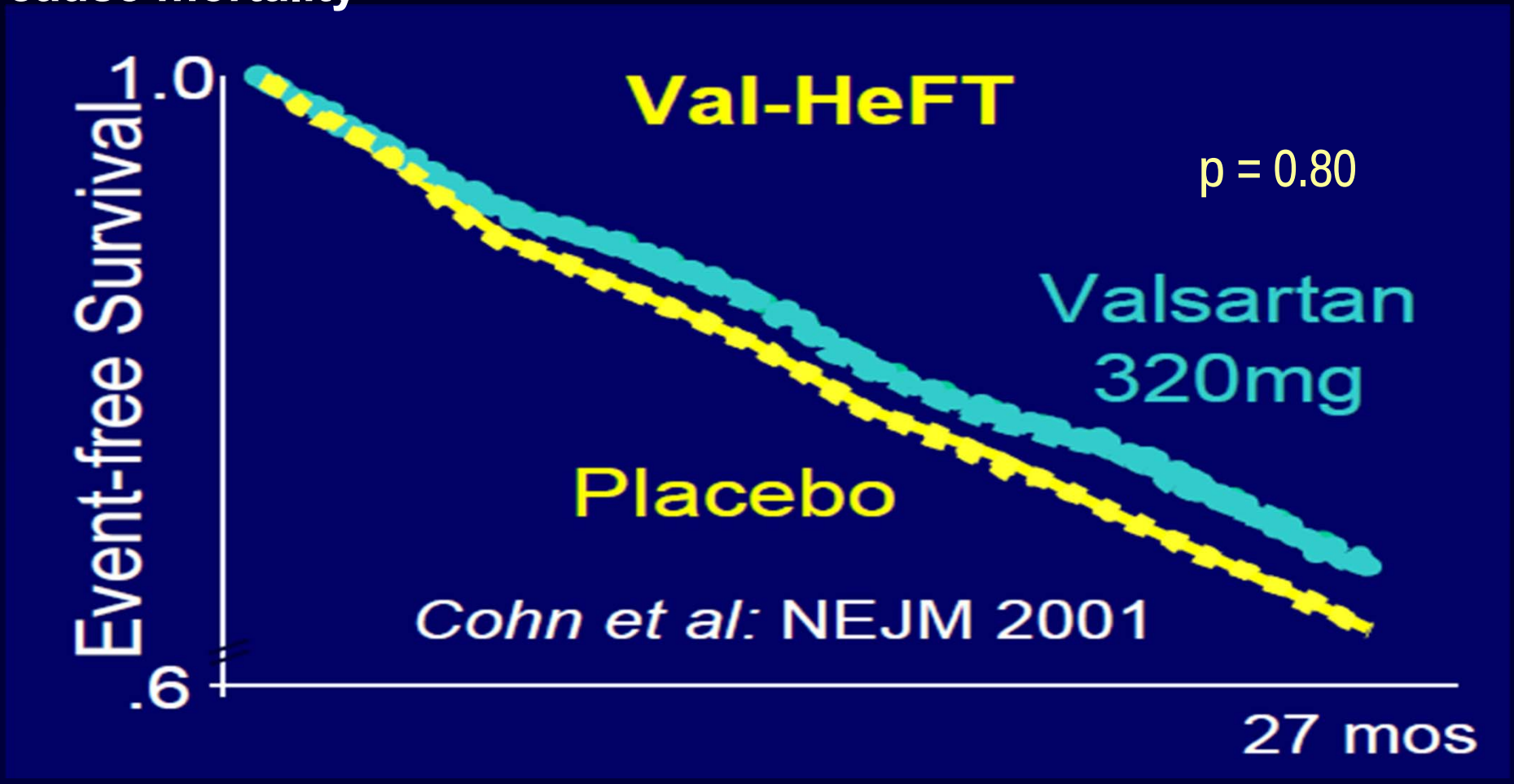


Considerations in ELITE-2 Study

- Primary endpoint : all-cause mortality
- ACEI – naive patients
- Low dose of ARB (losartan, 44 mg) ?
- High prevalence of ACEI (captopril) discontinuation ?
- How about long-acting ACEI ?

ARBs in Heart Failure

All-cause mortality



Considerations in Val-HeFT Study

- Two primary endpoints

1) all-cause mortality
2) combined endpoints of all-cause mortality/CV morbidity

- ACEI – tolerant patients

- High dose of ARB (valsartan, 254 mg) ?

- Beta-blockers (35 %), ACEI (93 %)

- Safety for high-dose of ARB ?

: 9.9 % of discontinuation

CHARM Programme

3 component trials comparing candesartan to placebo in patients with symptomatic heart failure

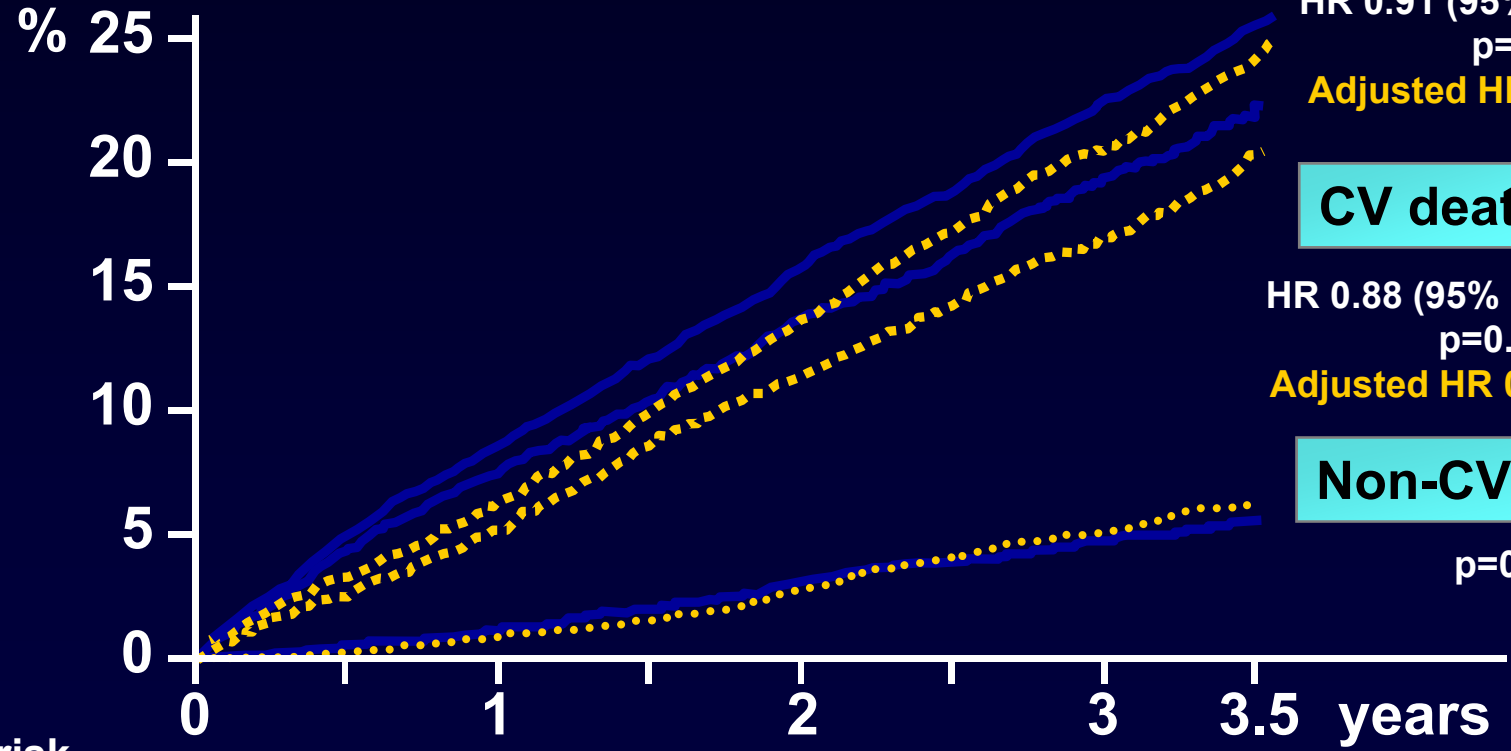
CHARM Alternative	CHARM Added	CHARM Preserved
n=2028	n=2548	n=3025
LVEF ≤40% ACE inhibitor intolerant	LVEF ≤40% ACE inhibitor treated	LVEF >40% ACE inhibitor treated/not treated

Primary outcome for each trial: CV death or HF hospitalisation

Primary outcome for Overall Programme: All-cause death

Lancet. 2003;362(9386):759-66

CHARM-Overall



All cause death

HR 0.91 (95% CI 0.83-1.00), p=0.055

Adjusted HR 0.90, p=0.032

CV death

HR 0.88 (95% CI 0.79-0.97), p=0.012

Adjusted HR 0.87, p=0.006

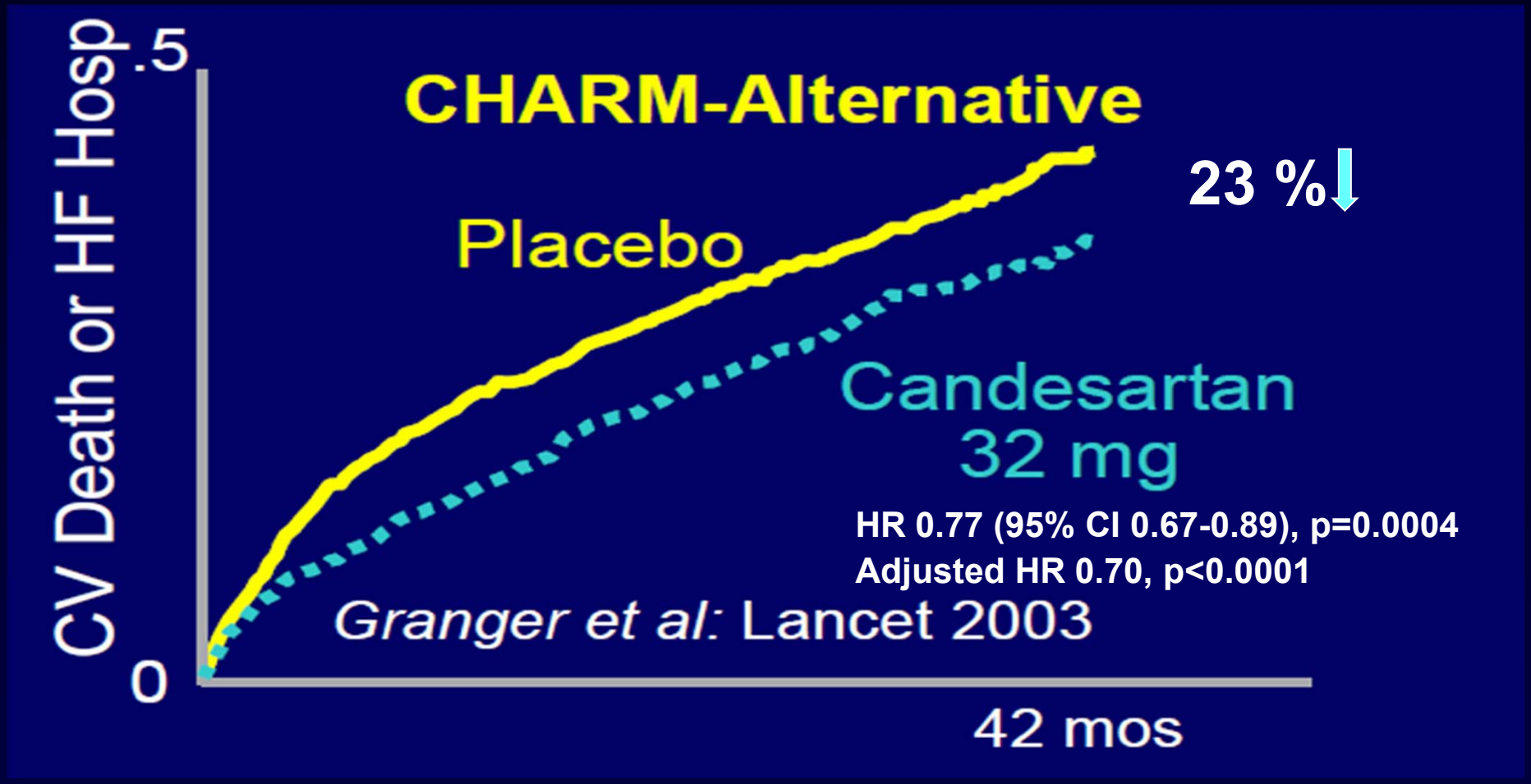
Non-CV death

p=0.45

Number at risk					
Candesartan	3803	3563	3271	2215	761
Placebo	3796	3464	3170	2157	743

Lancet. 2003;362(9386):759-66

ARBs in Heart Failure



Considerations in CHARM-Alternative Study

- ACEI – naïve patients
- HF patients on optimal standard therapy
- Relatively low CV risk factors
- Different primary endpoints
: (CV death or HF hospitalization)

ARBs in Heart Failure
CHARM-Added

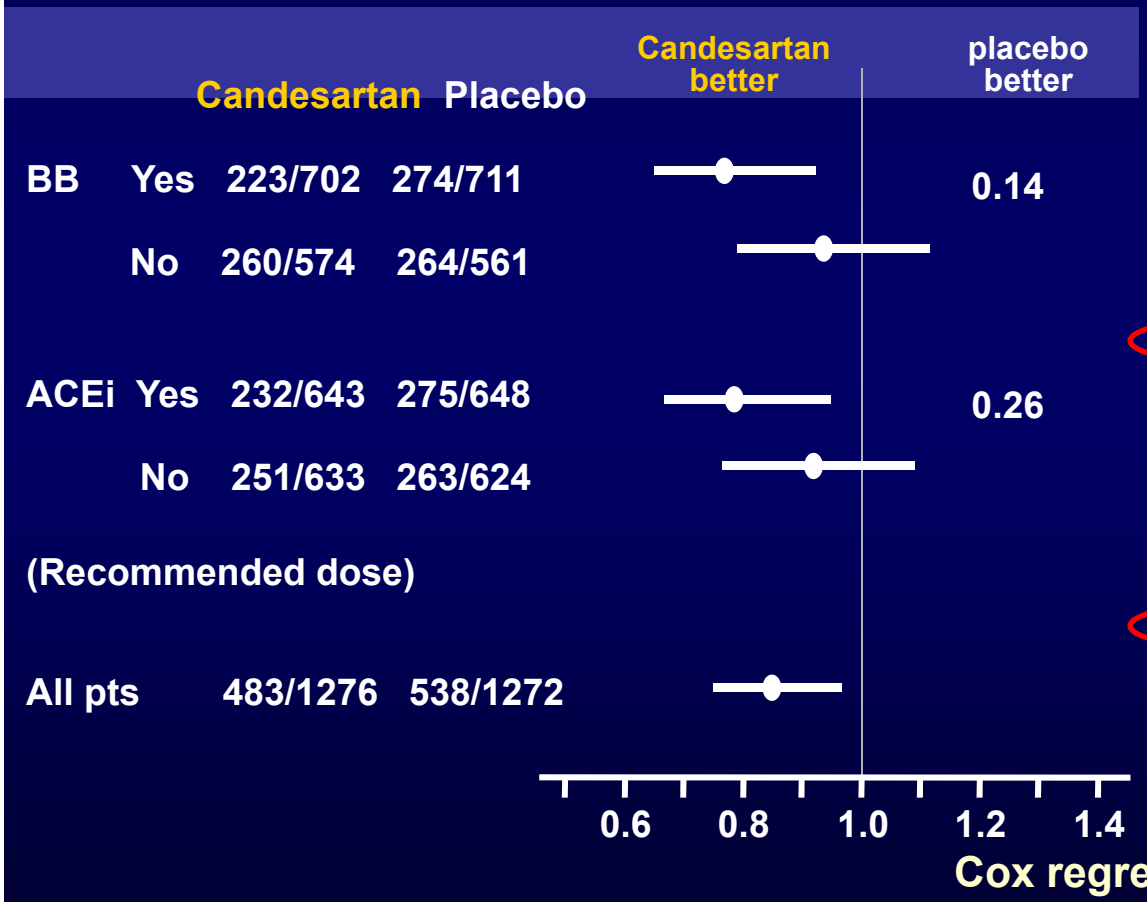
	Candesartan (n=1278)	**Placebo** (n=1272)	**Unadjusted HR (95% CI)**	**P**
CV death or hospital admission for CHF	37.9 %	42.3%	0.85 (0.75 - 0.96)	0.011
CV death	23.7%	27.3%	0.84 (0.72 - 0.98)	0.029
Hospital admission for CHF	24.2%	28.0%	0.83 (0.71 - 0.96)	0.014

Considerations in CHARM-Added Study

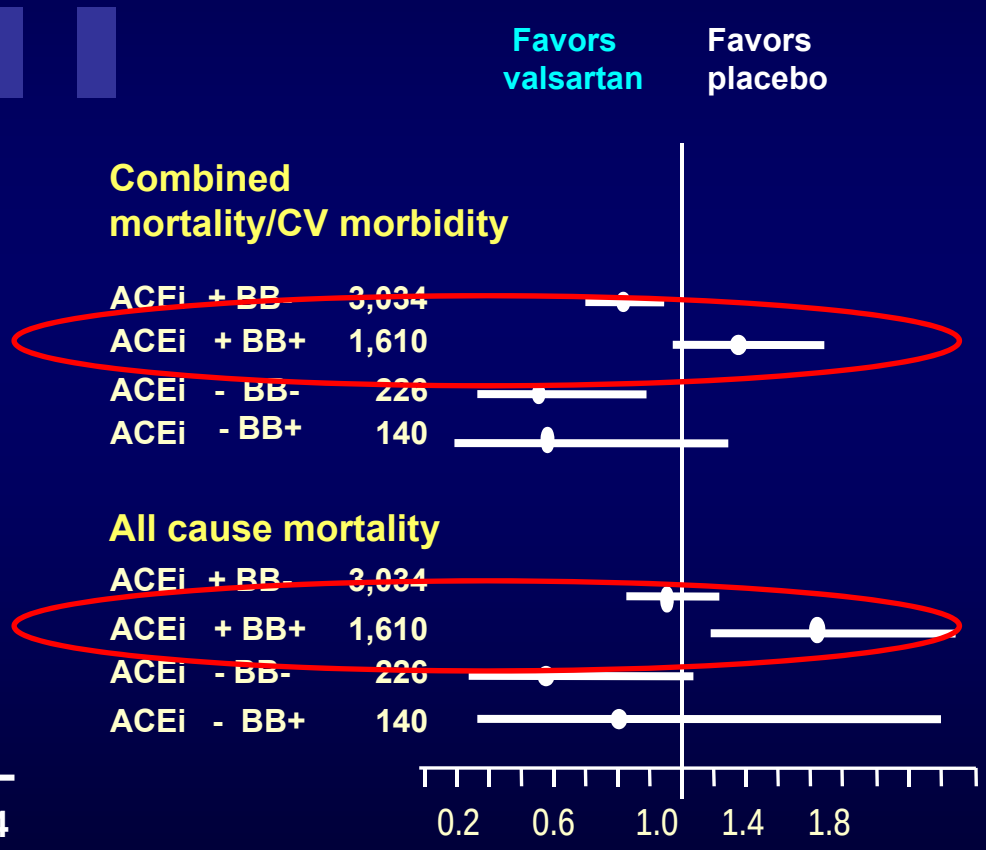
- ACEI – tolerant patients
- 96 % of ACEIs optimal dose
- Beta-blockers (55%), spironolactone (17%)
- Different primary endpoints
: (CV death or HF hospitalization)

Add-on therapy for heart failure patients

CHARM-Added [1)]

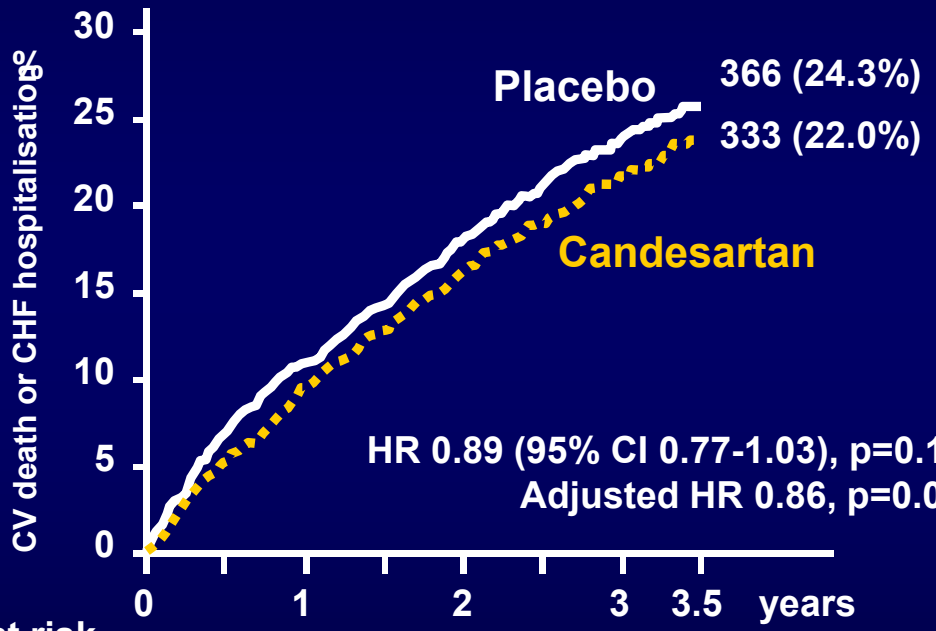


Val-HeFT [2)]



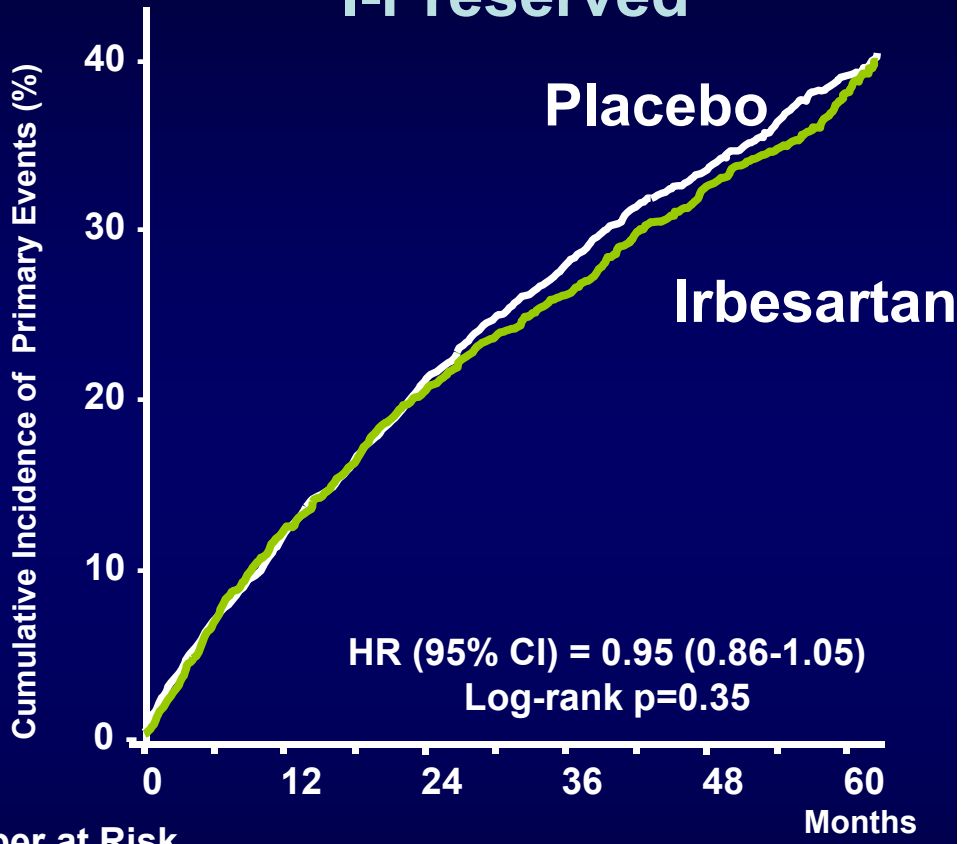
Preserved heart failure patients

CHARM-Preserved



Number at risk					
Candesartan	1514	1458	1377	833	182
Placebo	1509	1441	1359	824	195

I-Preserved



Number at Risk						
Irbesartan	2067	1812	1640	1513	1088	497
Placebo	2061	1808	1618	1466	1051	446

Lancet. 2003 Sep 6;362(9386):777-81.

Heart Failure Indication

	Candesartan	Valsartan	Irbesartan Losartan Olmesartan Telmisartan
Indication	O	O	X
	• **ACEi**에 내약성이 좋지 않은 경우 • **ACEi**에 추가요법이 필요한 경우	**ACEi**에 불내성인 심부전	
용법 용량	**1일 1회** 4~32mg	**1일 2회** 1회 40mg, 1회 80~160mg	
주의사항		• ACEi, BB, Valsartan의 **3중 요법은 권장되지 않는다.** • **중증 심부전 환자에게** ACEi 또는 ARB로 치료하는 것은 빈뇨, 진행성 질소혈증, 급성신부전 또는 사망과 관련이 있다.	

Different ARBs have NOT been tested head to head in HF patients !

Association of Candesartan vs Losartan with All-cause Mortality in Patients with Heart Failure

JAMA 2011;305:175-82.

Backgrounds

- ARBs reduce combined mortality and hospitalization in patients with HF with reduced LVEF.
- Different agents have different affinity for the AT_1 receptor and may have different clinical effects.
- RCTs have NOT been performed to test difference of ARBs efficacy in HF patients.

Objective

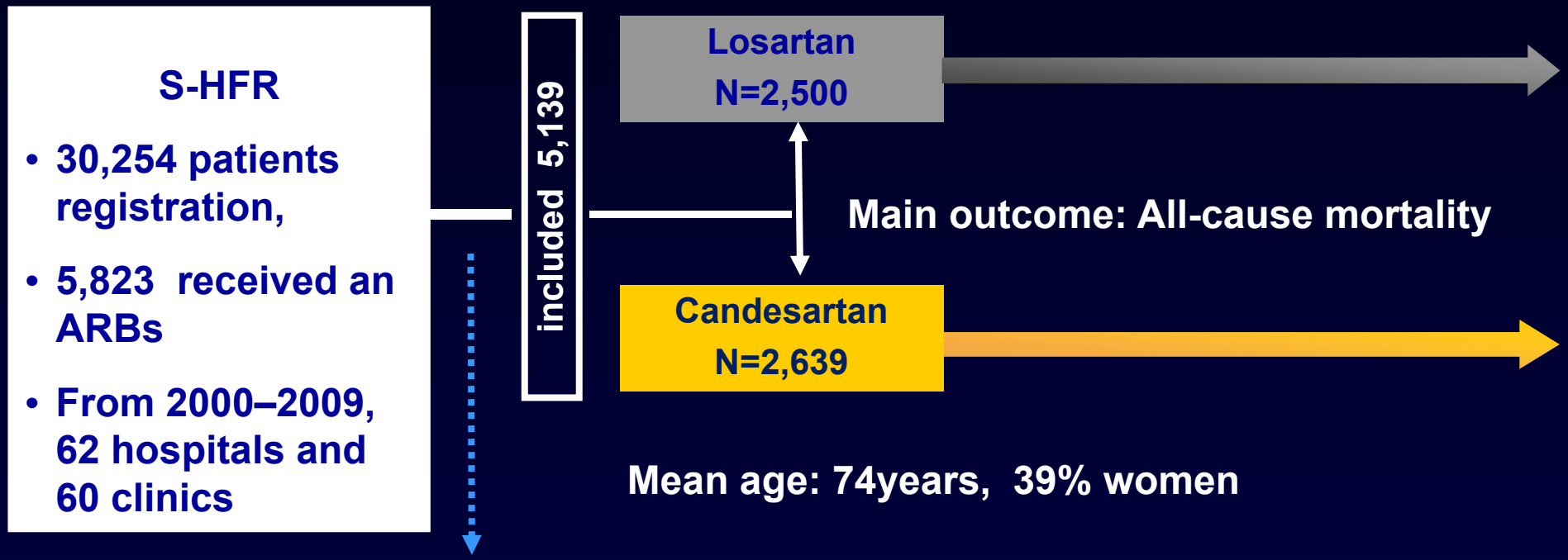
- To determine whether candesartan is associated with all-cause mortality than losartan in a large cohort of unselected patients with HF

Methods

Swedish Heart Failure Registry (RisksSvikt, S-HFR)

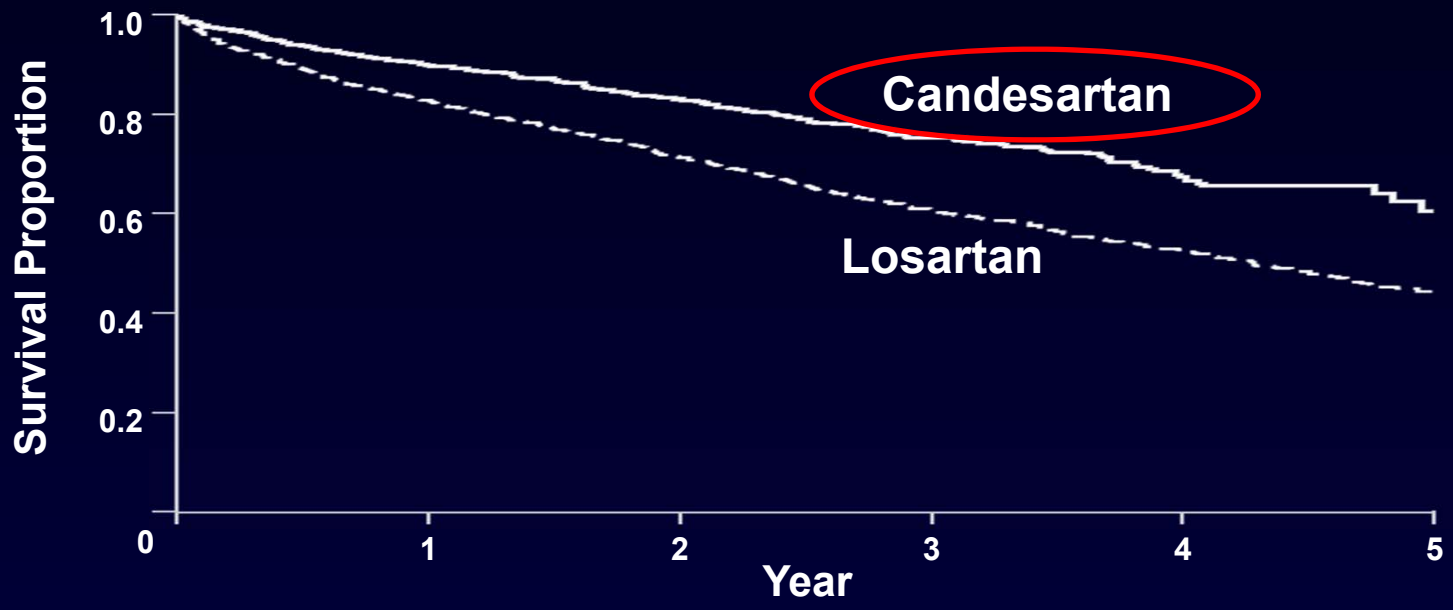
- Inclusion criteria are clinician-judged HF.
- Approximately 70 variables are recorded at discharge from hospital or after clinic visit on a case record form
- Main outcome: all-cause mortality
- Statistical anlalysis
  - To ajdust for selection bias, propensity scores for each patient were estimated with logistic regression
  - Kaplan-Meier survival analysis and log-rank test by LVEF

Design



Valsatan (n=357) and other ARBs (n=327) were excluded due to small numbers

Results: Overall Suvival



No. at risk						
Candesartan	2639	1739	957	426	125	30
Losartan	2500	1692	1097	646	359	178

- **1 year survival**
  Candesartan group *90%* vs. losartan group *83%*

- **5 year survival**
  Candesartan group *61%* vs. losartan group *44%* (log-rank P< .001)

Results: HRs for all-cause mortality

Proportinal hazard regression models for all-cause mortality for Losartan vs Candesartan

Losartan vs. Candesartan	HR (95% CI)
Univariate model	1.77 (1.58-1.99)
Multivariate model	
Adjusted for age and sex	1.56 (1.39-1.75)
Adjusted for duration of heart failure	1.71 (1.52-1.92)
Adjusted for hypertension	1.77 (1.58-1.99)
Adjusted dose of 50 mg/d[b]	2.53 (2.22-2.88)
Adjusted dose of 150 mg/d[c]	1.91 (1.67-2.18)
Adjusted for ACE inhibitor, β-blocker, and aldosterone antagonist	1.71 (1.52-1.93)

Losartan vs. Candesartan	HR (95% CI)
Multivariate final model	
Final	**1.43 (1.23-1.65)**
With propensity scores covariate	1.41 (1.22-1.64)
With propensity scores strata	1.43 (1.23-1.65)

- ***Univariate HR: 1.77 (95% CI 1.58-1.99)***
- ***Multivariate HR including stratification for propensity score: 1.43 (95% CI 1.23-1.65, P < .001), HR= 0.70 for candesartan vs losartan***

Results: HRs after adjustment

Multivariate final analysis with propensity score strata and interaction for patients receiving losartan vs candesartan

Multivariate Final Analysis	HR (95% CI)	P Value	
		Main Effect	Interaction
β-Blocker			
No	1.90 (1.39-2.60)	<.001	.04
Yes	1.35 (1.15-1.57)	<.001	.04
Cardiac resynchronization therapy			
No	1.45 (1.25-1.68)	<.001	.09
Yes	0.82 (0.42-1.58)	.55	.09
Duration of heart failure, mo			
No	1.72 (1.35-2.20)	<.001	.05
Yes	1.33 (1.12-1.56)	<.001	.05
Creatinine	1.51 (1.18-1.93)	<.001	.07
Lung disease			
No	1.52 (1.29-1.79)	<.001	.06
Yes	1.17 (0.90-1.51)	.24	.06

Losartan remained associated with increase mortality compared with candersartan for all categories *except cardiac resynchronization therapy and lung disease.*

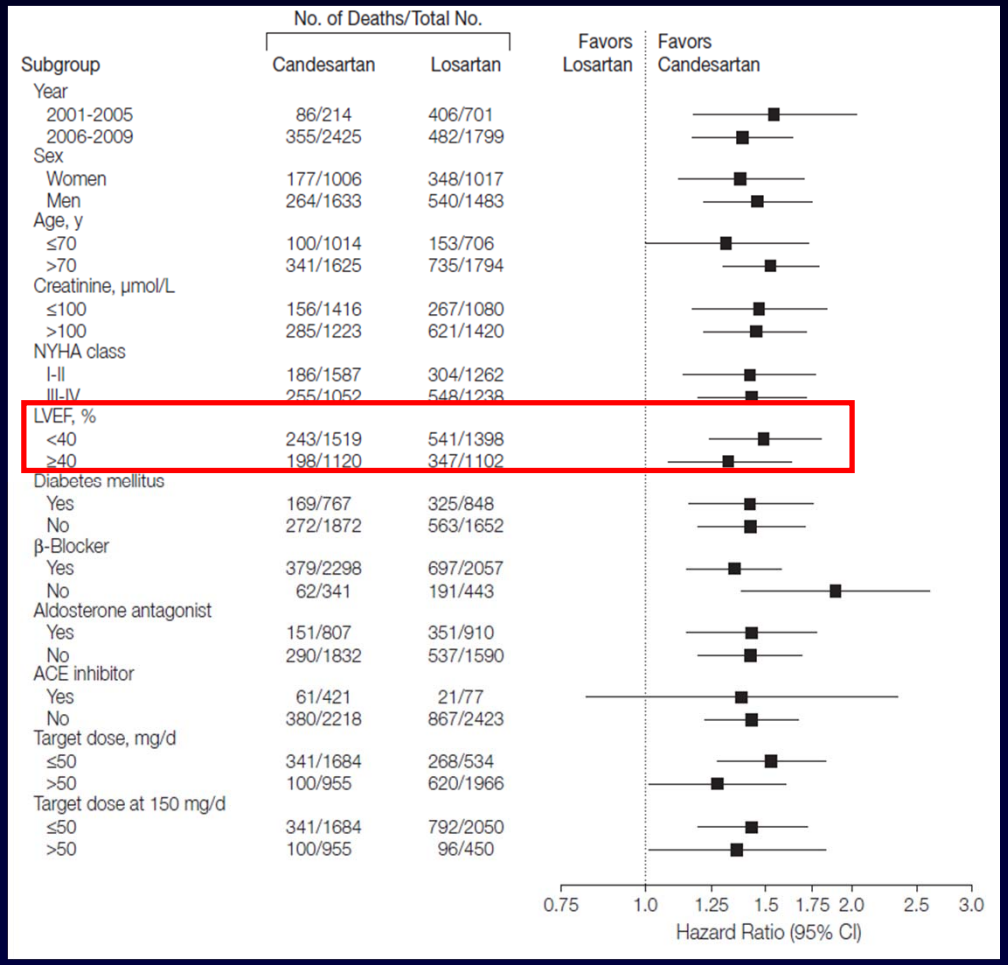
Results: HRs in subgroup

HRs for all-cause mortality from multivariate model after adjustment with selected subgroups

Subgroup	No. of Deaths/Total No.	
	Candesartan	Losartan
Year		
2001-2005	86/214	406/701
2006-2009	355/2425	482/1799
Sex		
Women	177/1006	348/1017
Men	264/1633	540/1483
Age, y		
≤70	100/1014	153/706
>70	341/1625	735/1794
Creatinine, μmol/L		
≤100	156/1416	267/1080
>100	285/1223	621/1420
NYHA class		
I-II	186/1587	304/1262
III-IV	255/1052	548/1238
LVEF, %		
<40	**243/1519**	**541/1398**
≥40	198/1120	347/1102
Diabetes mellitus		
Yes	169/767	325/848
No	272/1872	563/1652
β-Blocker		
Yes	379/2298	697/2057
No	62/341	191/443
Aldosterone antagonist		
Yes	151/807	351/910
No	290/1832	537/1590
ACE inhibitor		
Yes	61/421	21/77
No	380/2218	867/2423
Target dose, mg/d		
≤50	341/1684	268/534
>50	100/955	620/1966
Target dose at 150 mg/d		
≤50	341/1684	100/955
>50	100/955	96/450

Results: HRs in subgroup

HRs for all-cause mortality from multivariate model after adjustment with selected subgroups



Candesartan vs losartan group in LVEF ≥40% patients

1 year Survival: 91% (95% CI 89-92%) vs 82% (95% CI 80-85%)

5 year Survival: 68%(95% CI 60-76%) vs 44% (95% CI 40-49%)

Candesartan vs losartan group in LVEF <40% patients

Univariate HR HR: 2.08 (95% CI 1.76-2.46% P<.001)

Multivariate HR including stratification for propensity score: 1.41 (95% CI 1.14-1.76% P=.002)

Conclusion

- Candesartan compared with losartan was associated with a lower mortality risk in this registry of patients with HF

Limitations

- The study was registry study not randomized controlled trial and had potential biases and confounders.
- Diagnosis of HF in S-HFR is clinical and does not require objective evidence of HF

Different ARB agents should be tested against each other in RCTs

ARBs Treatment in HF patients

- Angiotensin II receptor blockers (ARBs) are widely used to treat heart failure (HF)

Reduction of mortality and hospitalization in patients with HF with reduced left ventricular ejection fraction.

- ARBs vary in their affinity for the AT_1 receptor and in their effects on blood pressure

ARBs, Are they really Same?

- BP control efficacy → Different
- Beyond BP control effect
  - Existence of Clinical Evidence → Different
  - Difference in Result → Different

경청해 주셔서
감사 합니다.