The benefits of RAS blockade in patients with CV disease

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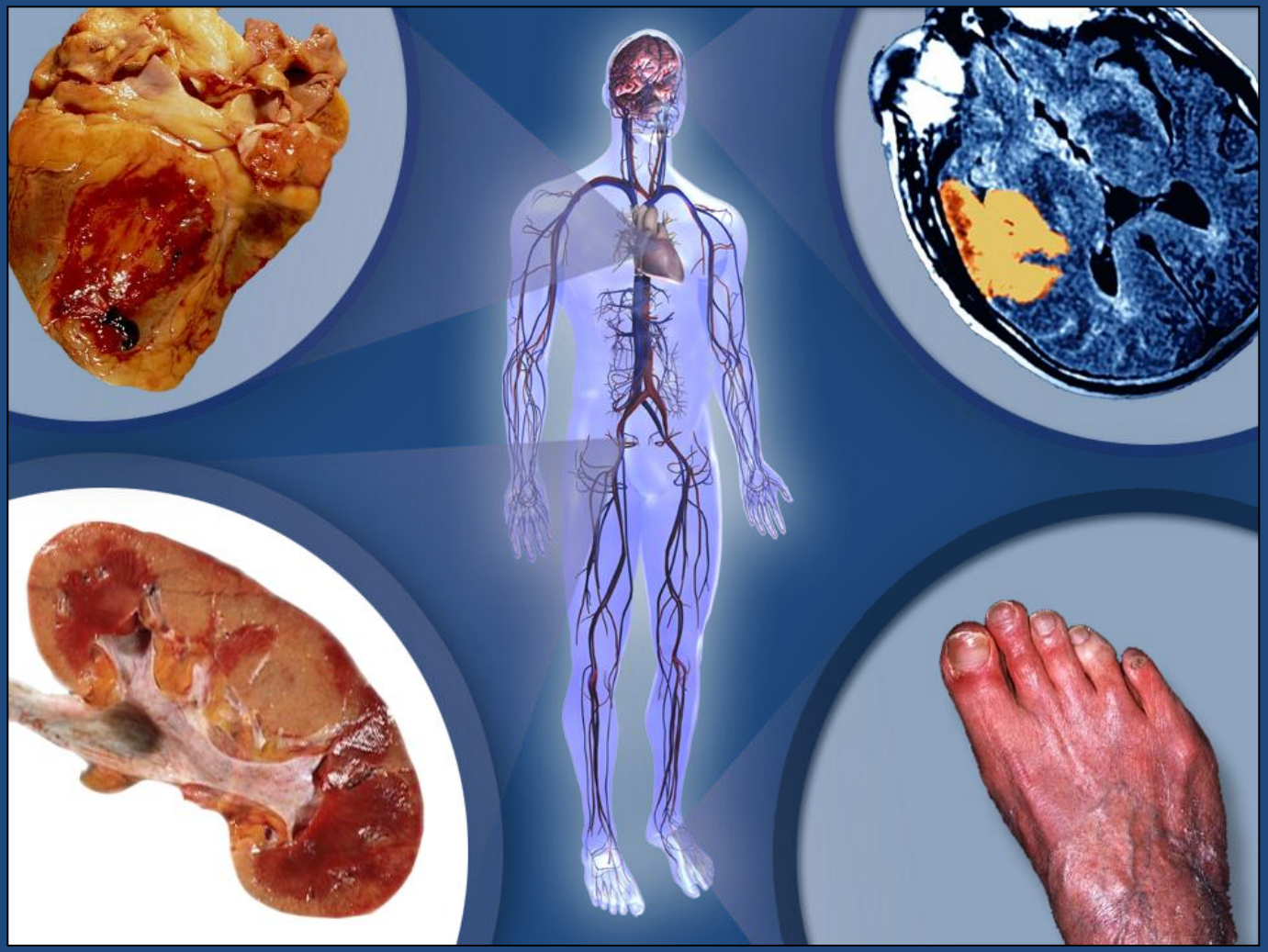
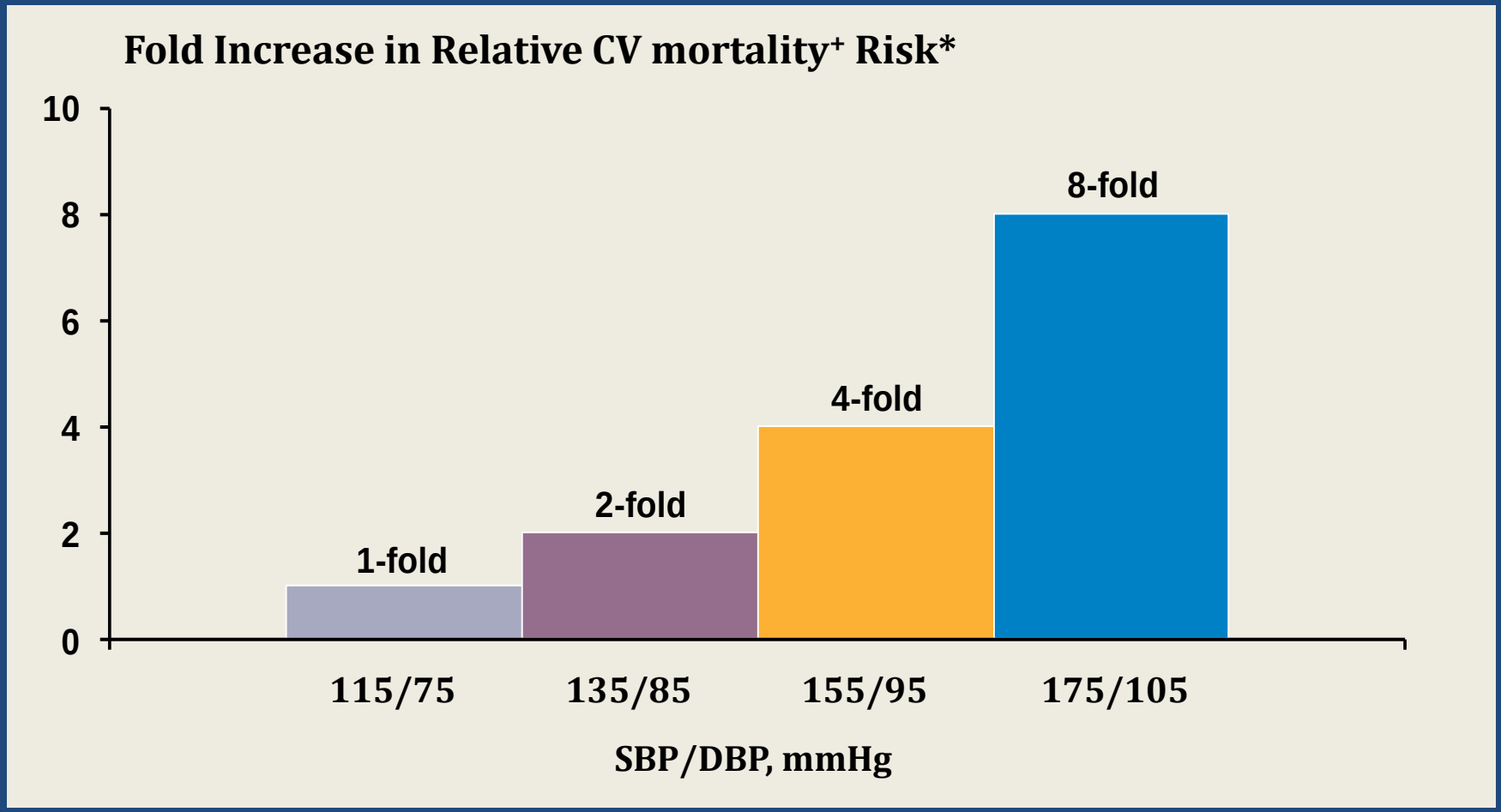
고혈압 합병증



Each 20/10 mmHg BP increase doubles the risk of CV mortality



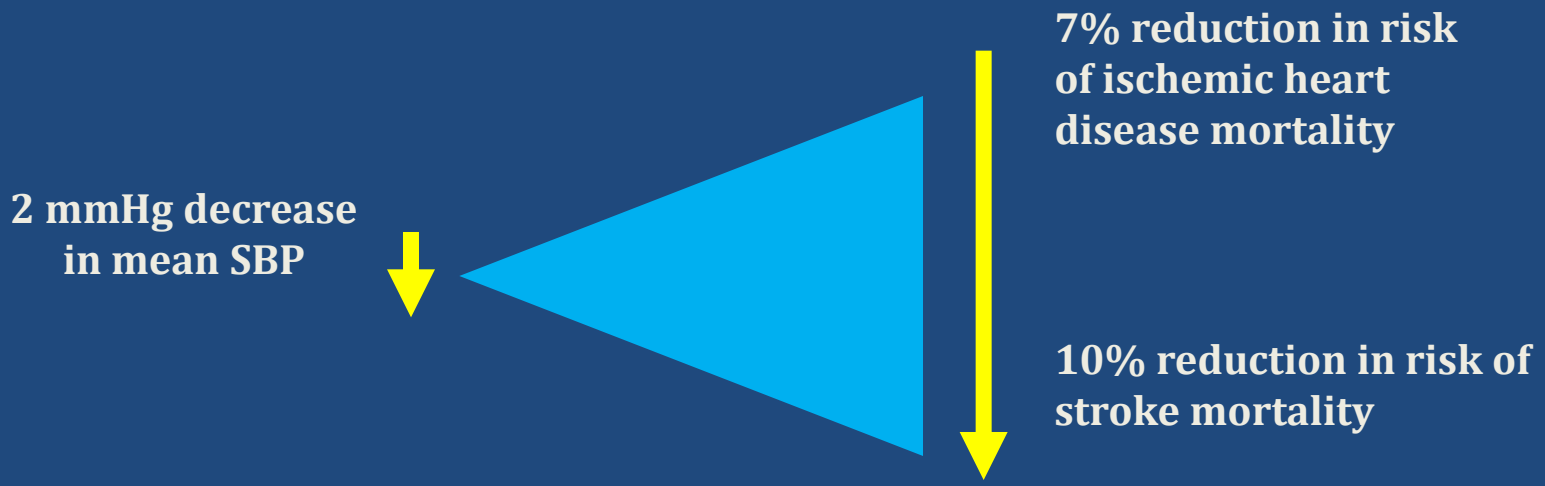
+ CV mortality: stroke death, death from IHD and from vascular death

* risk Individuals aged 40–69 years (N = 1 million).

Lewington S, et al. Lancet. 2002;360:1903–1913.

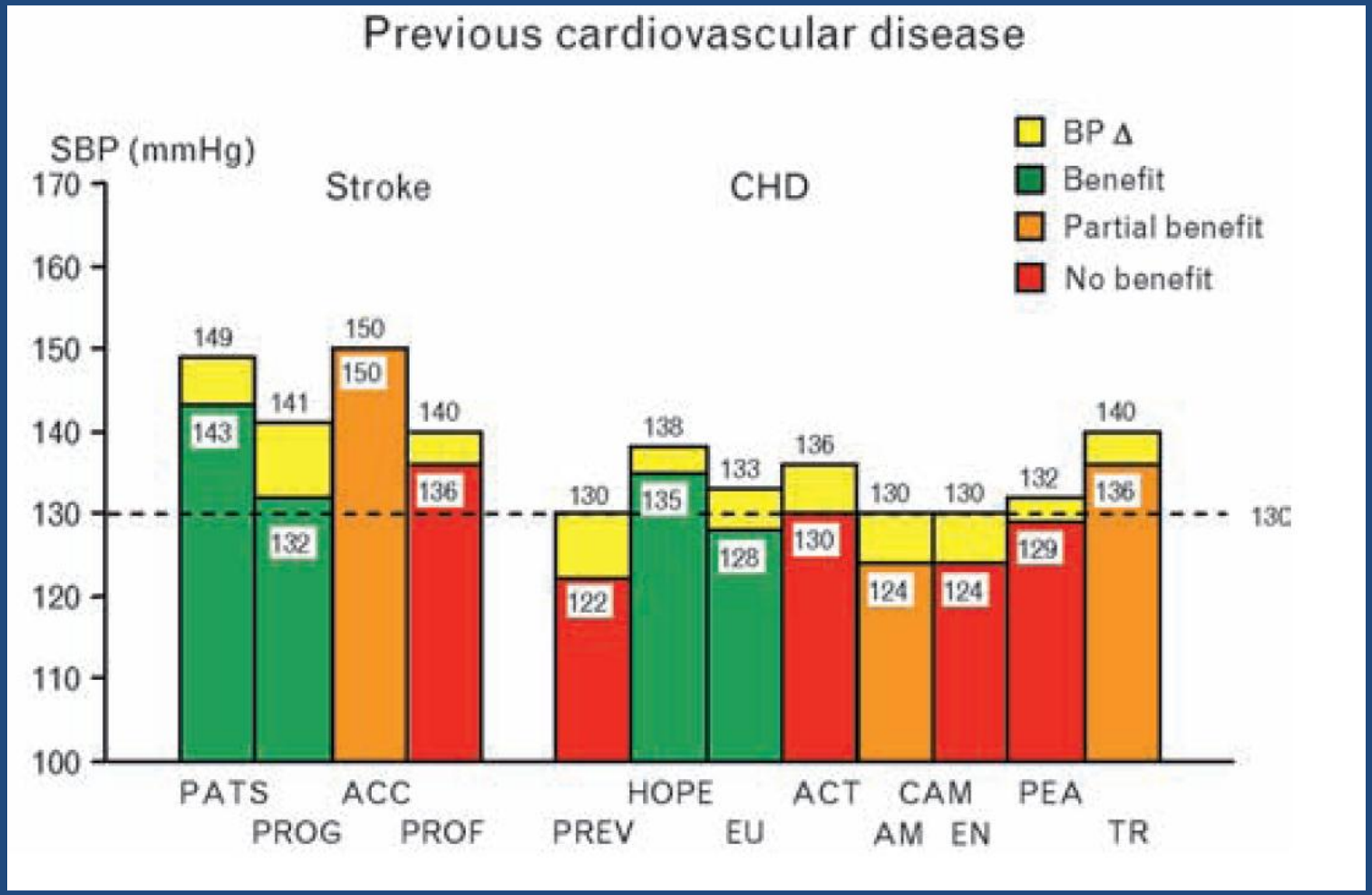
Blood Pressure Reduction of 2 mmHg Decreases the Risk of Cardiovascular Events by 7–10%

- Meta-analysis of 61 prospective, observational studies
- 1 million adults
- 12.7 million person-years



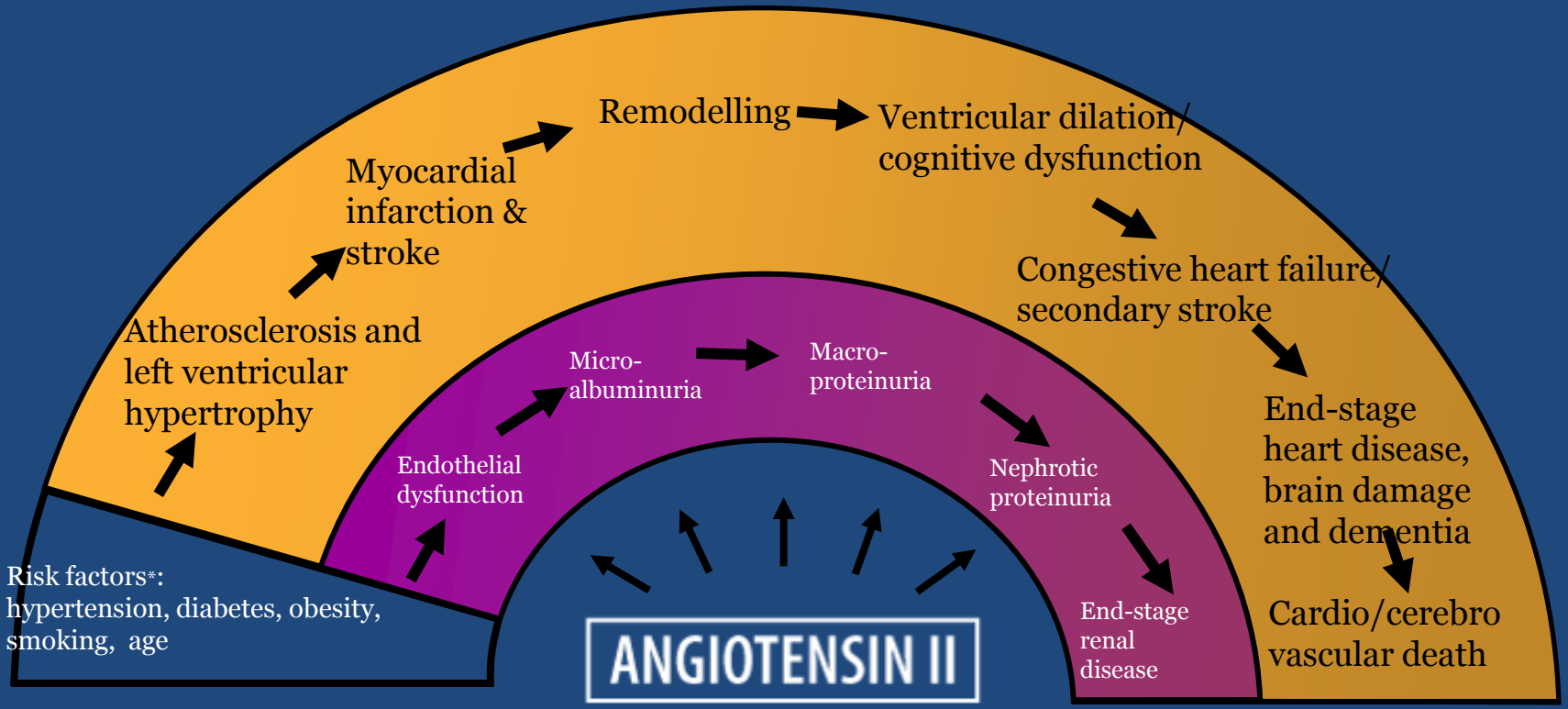
Lewington et al. Lancet 2002;360:1903–13

Beyond blood pressure lowering effect ?



Zanchetti, *et al., J HT 2008*

The cardiovascular (CV) continuum: role of risk factors and angiotensin II

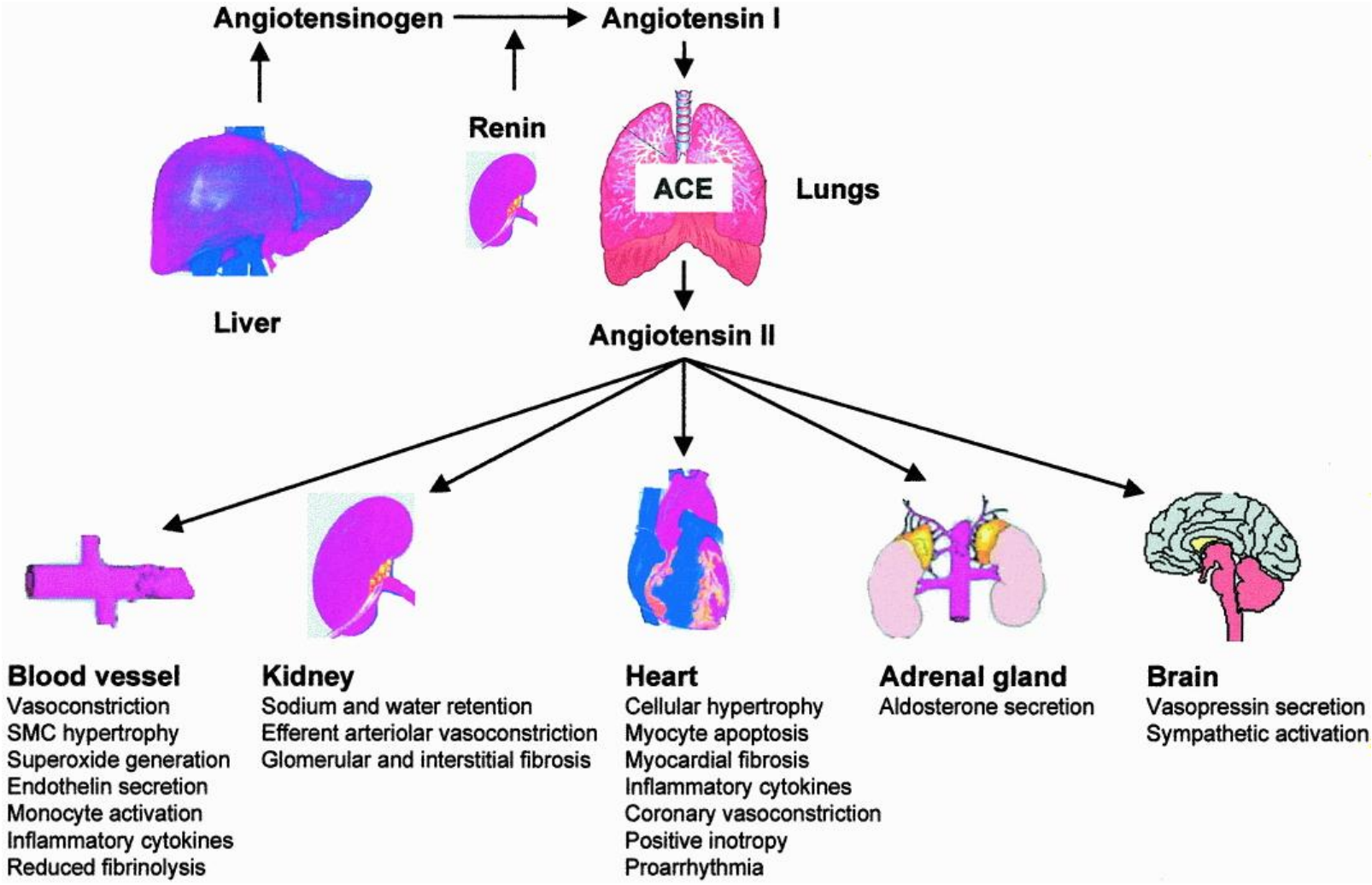


- *Intervention at any point along the chain of events may modify cardiovascular disease progression and provide cardioprotection*

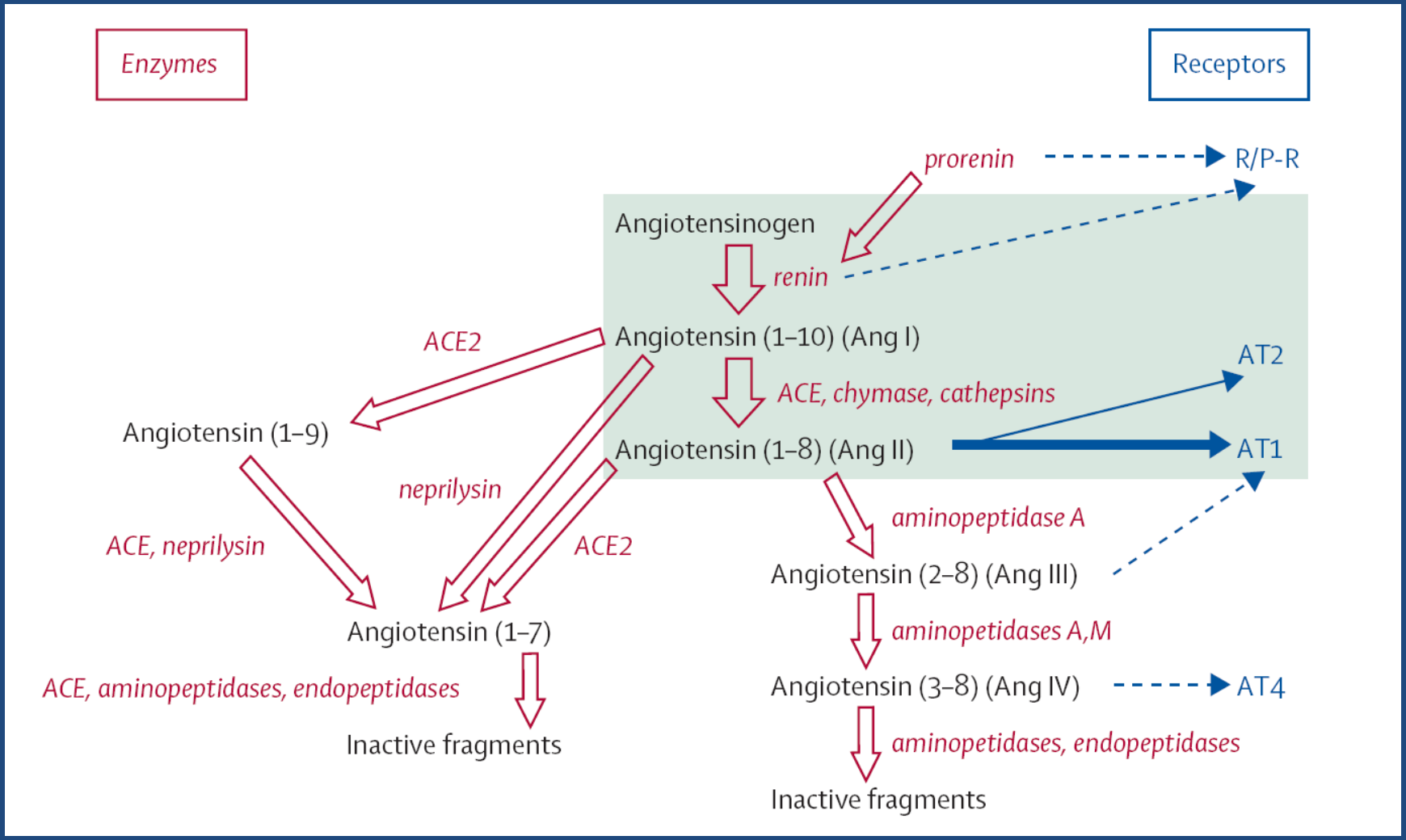
**An additive effect of risk factors has been shown in the risk for a CV event*

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

Renin-Angiotensin System



Overview of the proteins, peptides, enzymes, and receptors of the renin-angiotensin system



Schmieder, et al., **Lancet 2007**

JNC-7

Hypertension associated with co-existing conditions

ESC 2007

Condition	Preferred drug	Other drugs that can be used	Drugs to be avoided
Diabetes mellitus	**ACEIs, ARBs** If needed add HCTZ (GFR > 50ml/min) & loop diuretic (GFR < 50ml/min)	**CCBs**	**Beta blockers**
Diabetic nephropathy	**ACEIs, ARBs** If needed add CCBs, beta blockers or diuretics	**CCBs, beta blockers or diuretics** (when ACEIs/ARBs are Contraindicated)	
Nephropathy (non-diabetic)	**ACEIs, ARBs, ACEI-ARB combination**	**CCBs, Beta blockers, Diuretics**	
ESRD/ proteinuria	**ACEIs, ARBs, loop diuretics**	**Beta blockers, CCBs**	
Previous stroke	**ARBs, ACEIs, diuretic, CCBs**	**Beta blockers**	
Angina pectoris	**ACEIs, Beta blockers, long acting CCBs**	**ARBs, Diuretics**	
Previous myocardial infarction	**Beta blockers, ACEIs, ARBs, Anti-aldosterone**	**Diuretics, CCBs**	
Left ventricular hypertrophy	**ACEIs, ARBs, CCBs**	**Diuretics, Beta blockers**	

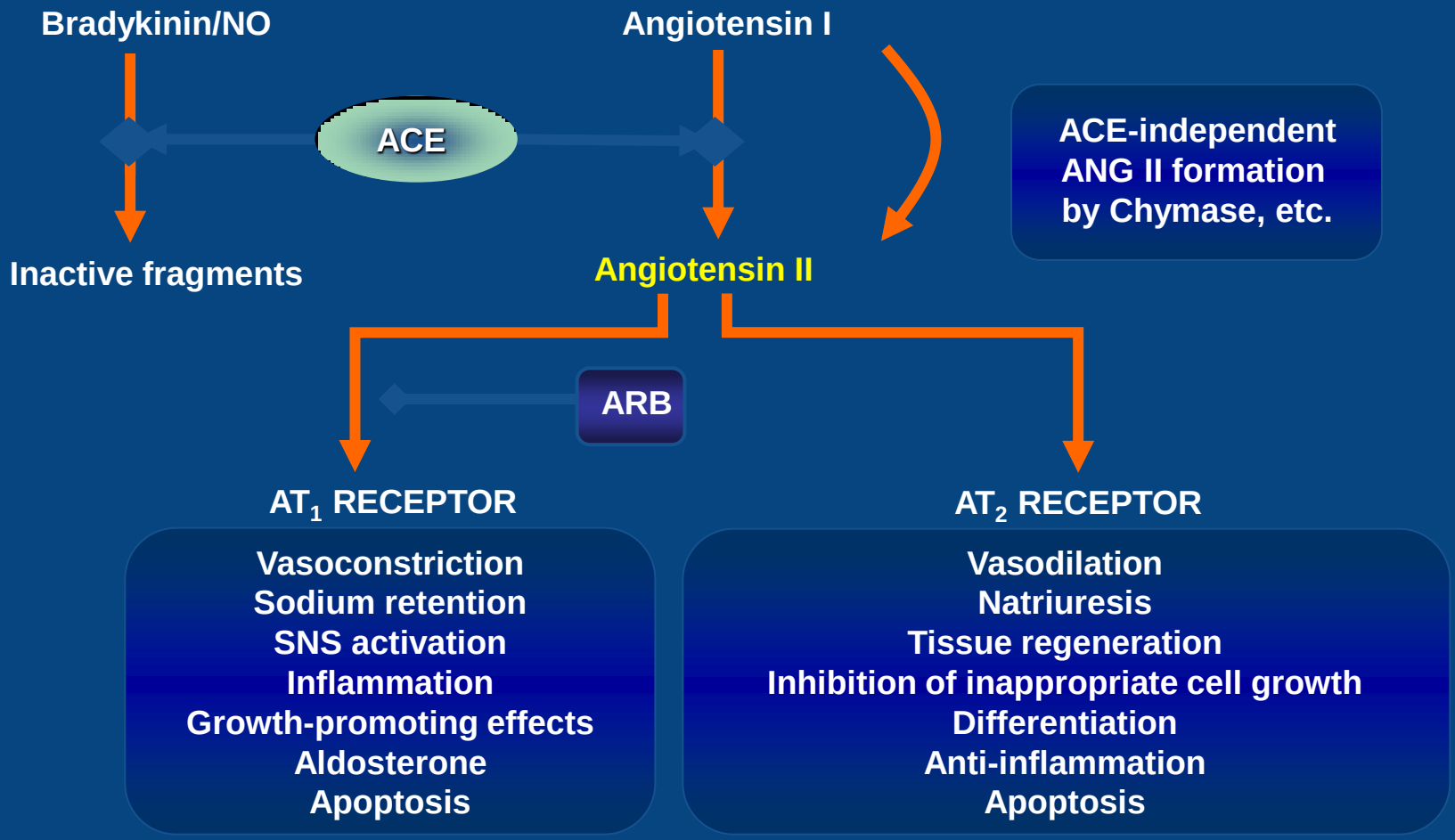
JNC-7

Hypertension associated with co-existing conditions

ESC 2007

Condition	Preferred drug	Other drugs that can be used	Drugs to be avoided
Left ventricular dysfunction	ACEIs	Beta blockers, diuretics, ARBs, CCBs	
Congestive heart failure	Diuretics, ACEIs, ARBs, Beta blockers, Anti-aldosterone		CCBs
Atrial fibrillation A) Recurrent B) Permanent	ARBs, ACEIs Beta blockers, non-DHP CCBs	Diuretics	
Peripheral arterial disease	ACEIs, CCBs	Diuretics, ARBs	Beta blockers
Metabolic syndrome	ACEIs, ARBs + combination with CCBs or low-dose HCTZ	Vasodilating beta Blockers	Non-vasodilating beta blockers + combination with HCTZ
High cholesterol level	ACEIs, ARBs, CCBs		Beta blockers, diuretics
Elderly	HCTZ, CCBs, ARBs, ACEIs, Beta blockers		
Isolated systolic hypertension	HCTZ, CCBs	ARBs, ACEIs, Beta blockers	

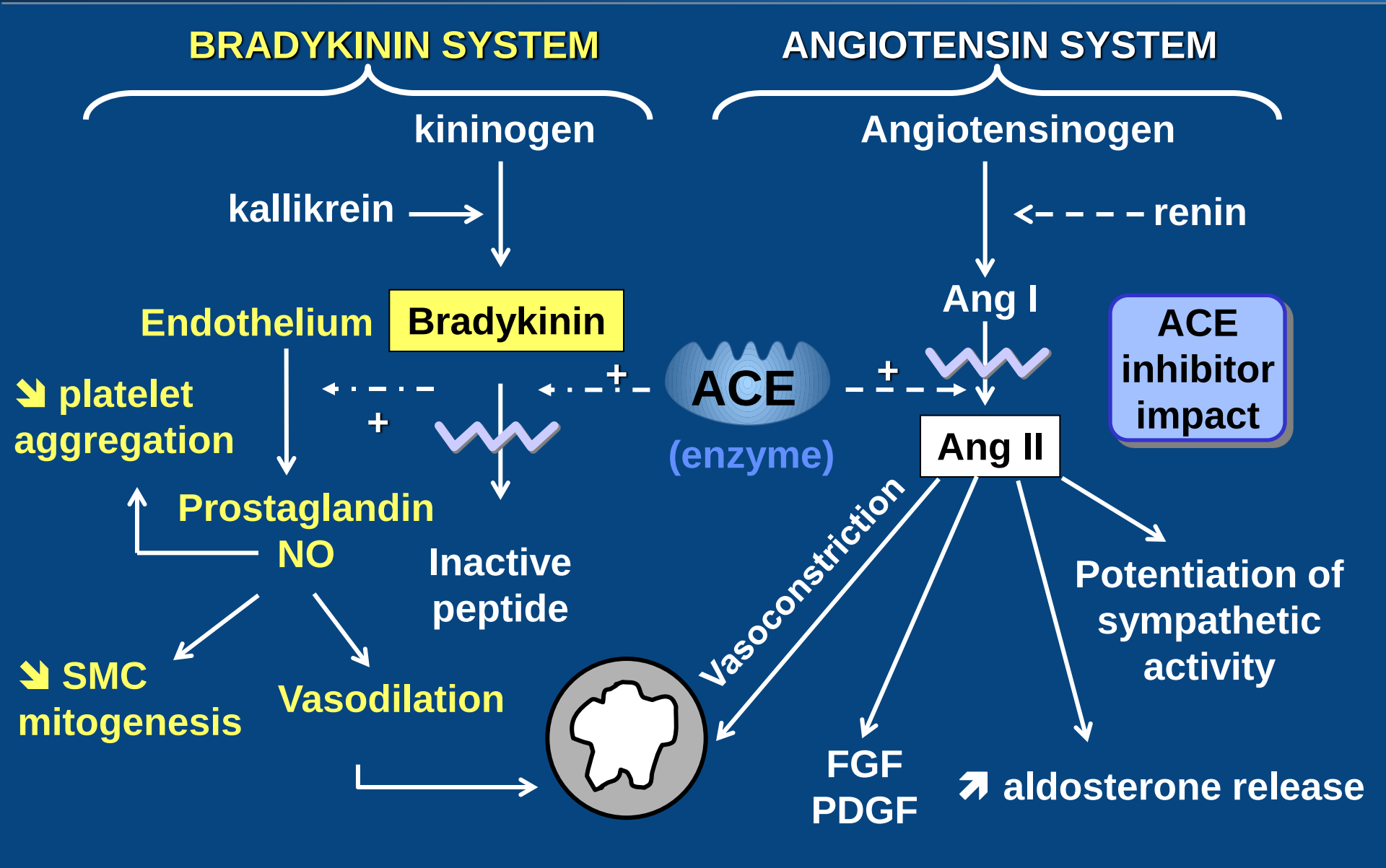
Mechanism of RAS inhibition



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

Hanon S, et al. J Renin Angiotensin Aldosterone Syst 2000;1:147–150;
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

ACE inhibitor is superior to ARB ?



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1. Benefits of RAS inhibitor

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- Mechanism of ACEI & ARB

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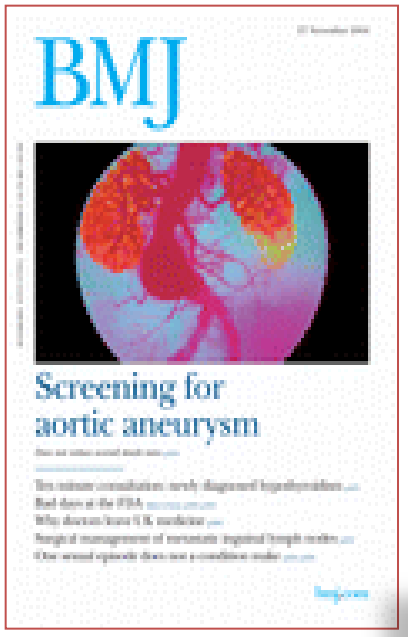
- Better antihypertensive effect with low dry cough
- Effect on MI, CHF, and LVH patients

Myocardial infarction and ARB

Article published in the British Medical Journal



Subodh Verma & Martin Strauss

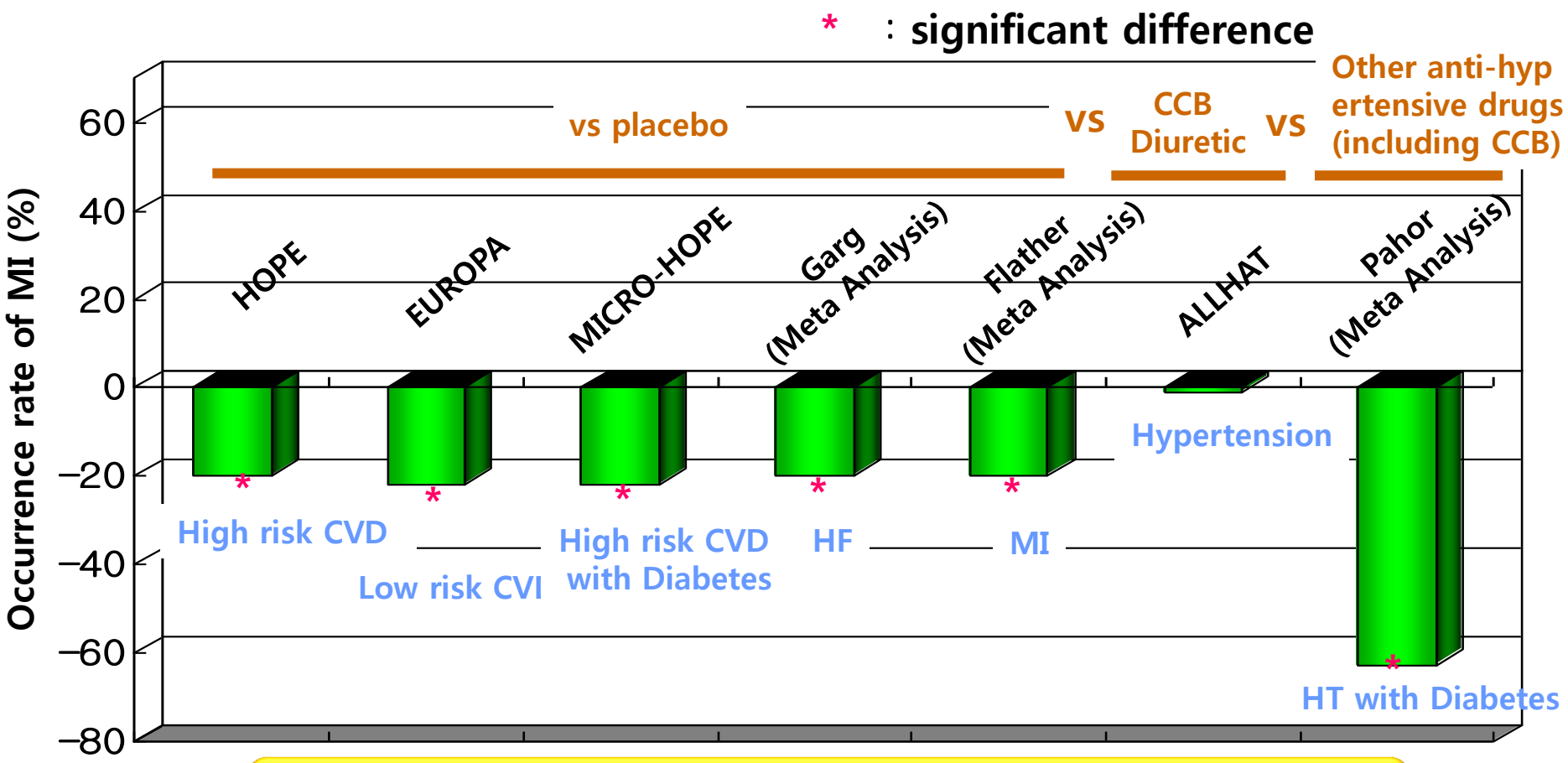
Angiotensin receptor blockers and myocardial infarction.

-These drugs may increase myocardial infarction and patients may need to be told -

2004년 BMJ에 "ARB가 심근경색을 증가시킬 수 있다" 라는 논문이 발표되면서 ARB & MI Paradox가 시작됨

BMJ 2004;329:1248-1249

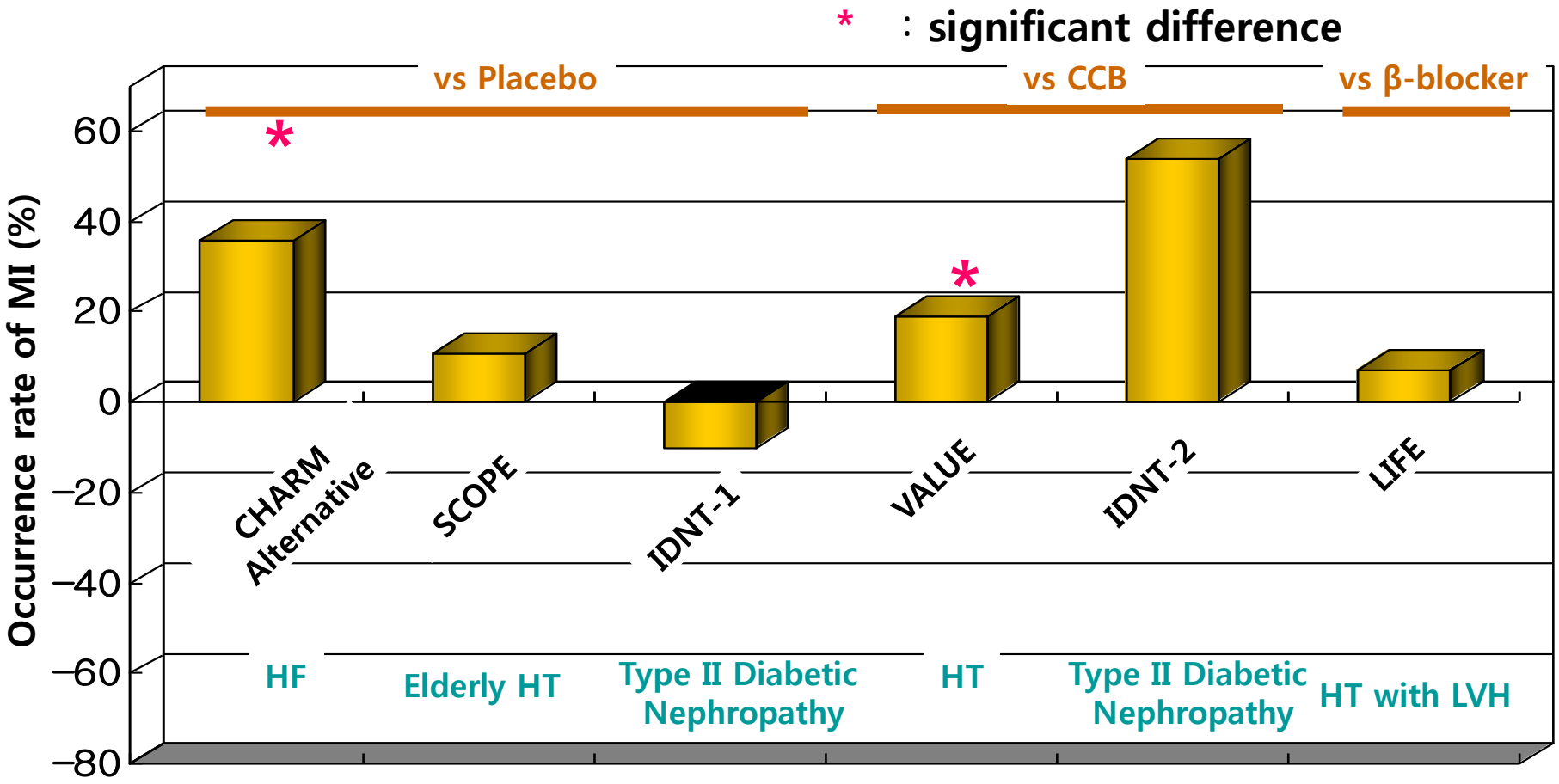
Myocardial Infarction risk of ACEI in Large Scale Clinical Studies



➢**ACE-Is significantly reduced the occurrence of MI.**

BMJ 2004;329:1248-1249 Ann Pharmacother. 2005 ;39:470-80

Myocardial Infarction risk of ARB in Large Scale Clinical Studies



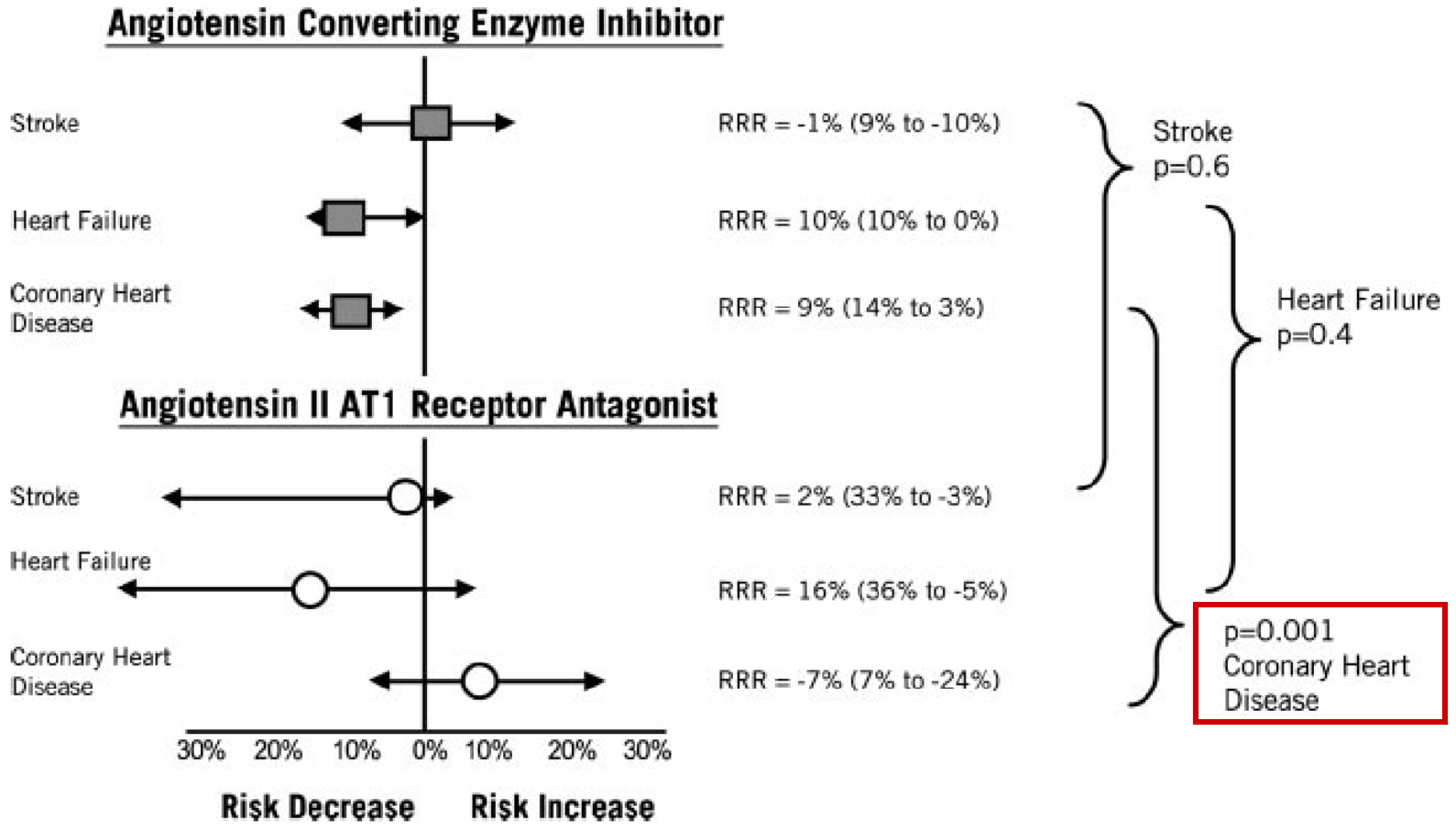
➢ARBs did not reduced the incidence of MI.
In some trials, ARBs significantly increased the occurrence.

BMJ 2004;329:1248-1249 Ann Pharmacother. 2005 ;39:470-80

BPLTTC Regression Meta-analysis

ACEis or comparators - AASK, ABCD(H), ABCD(N), ALLHAT, ANBP2, CAPPP, DIAB-HYCAR, EUROPA,, HOPE, JMIC-B, PART-2, PEACE, PROGRESS, SCAT, STOP-2, and UKPDSHDS

ARBs or comparators - IDNT, LIFE, RENAAL, SCOPE, and VALUE.



Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association. Learn and Live.
2006;114;838-854

ARB may Increase MI? : Biological Plausibility

ARBs bind the AT1 receptors and prevent Angiotensin II activation

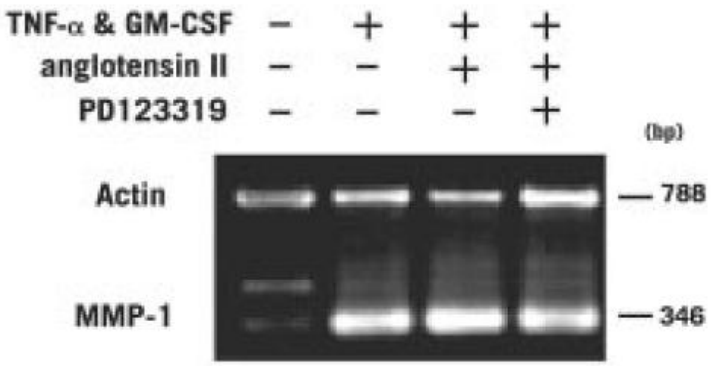
increase Ang II levels several-fold above baseline

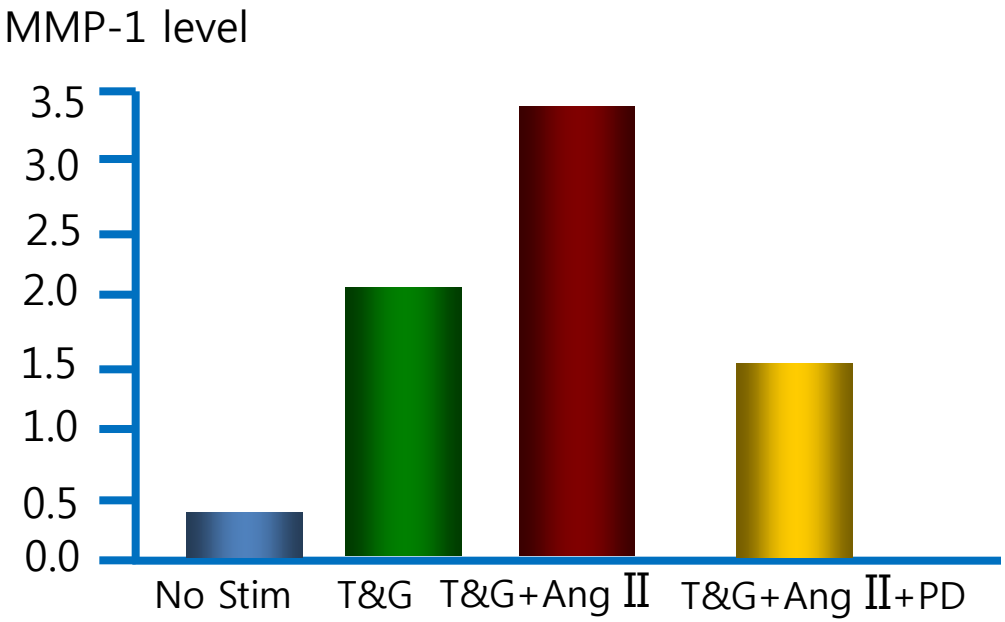
unopposed stimulation of the AT2 / AT4 receptor

Overexpression of Ang II

beneficial
or
harmful ?

AT-2 receptor promote plaque rupture by augmenting MMP-1



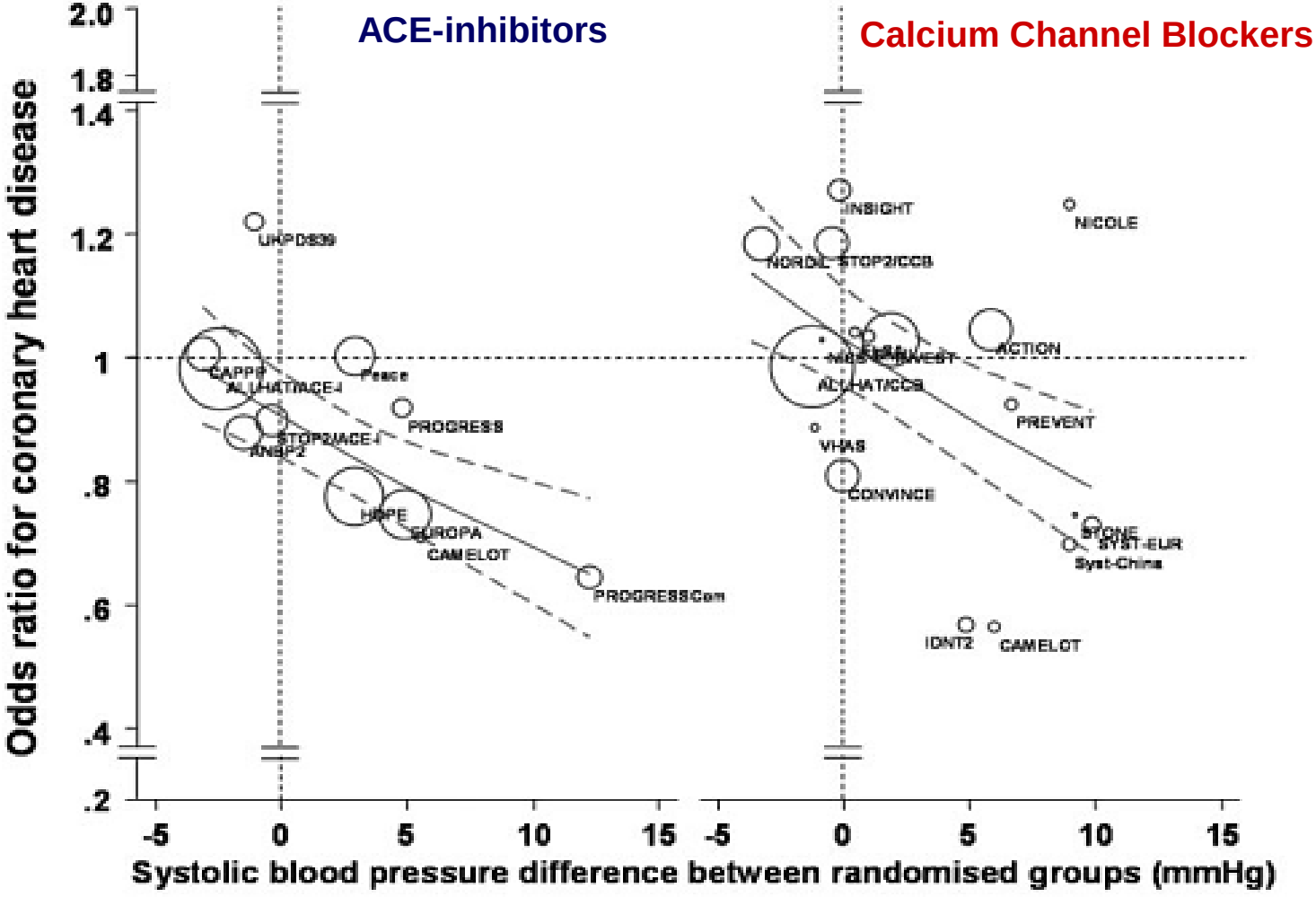


Ang II, through AT2 receptors and cyclooxygenases, plays a central role in production of MMP-1 by monocytes stimulated with tumor necrosis factor (TNF)-a and GM-CSF (granulocyte macrophage-colony stimulating factor), which may lead to atherosclerotic plaque rupture.

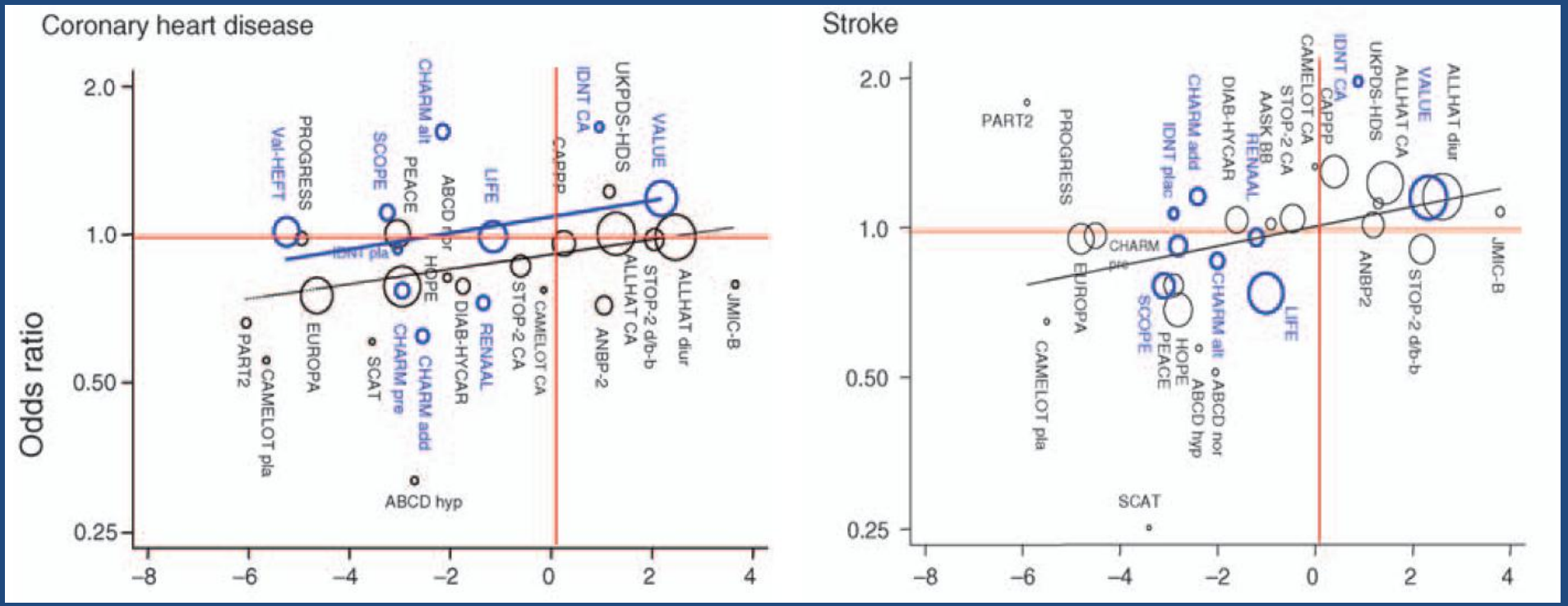
AT2 receptor antagonist PD decreases the ratio of MMP-1 to b-actin transcription in monocytes stimulated with TNF-a (T) and GM-CSF (G) plus Ang II

J Leukoc Biol. 2005;78:195–201.

ACE inhibitor; Better for CHD



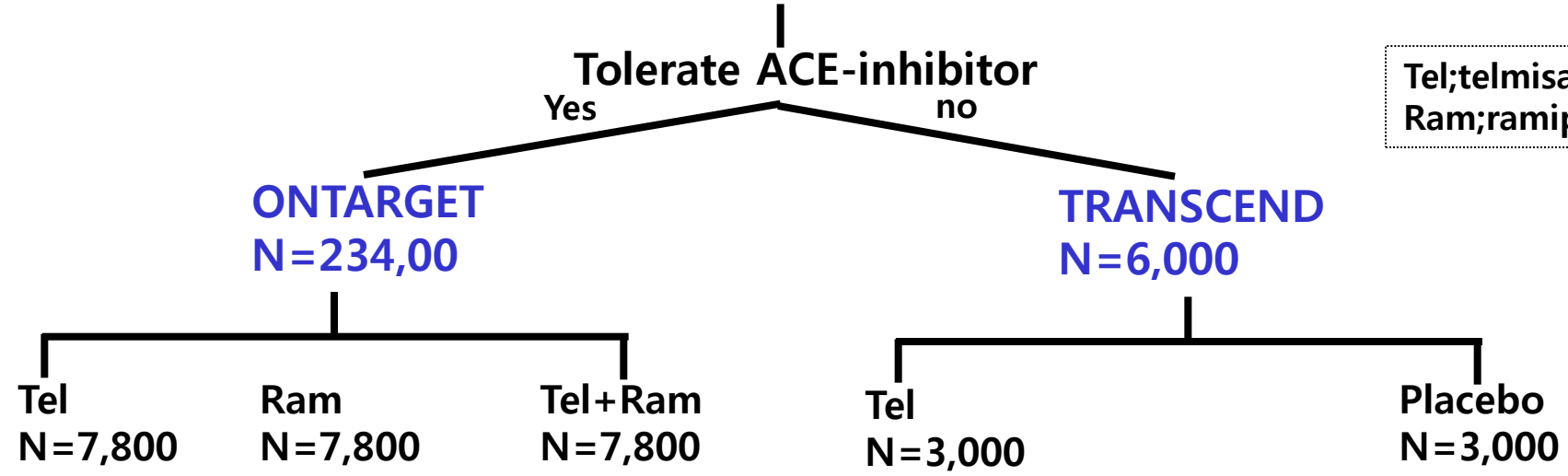
Blood pressure-dependent & independent effects of agents that inhibit RAS



Blood Pressure Lowering Treatment Trialists' Collaboration, ***J Hypertens 2008***

ONTARGET/TRANSCEND trials

High-risk patients with previous vascular event or DM with target organ damage but controlled BP and no heart failure.



Tel;telmisartan
Ram;ramipril

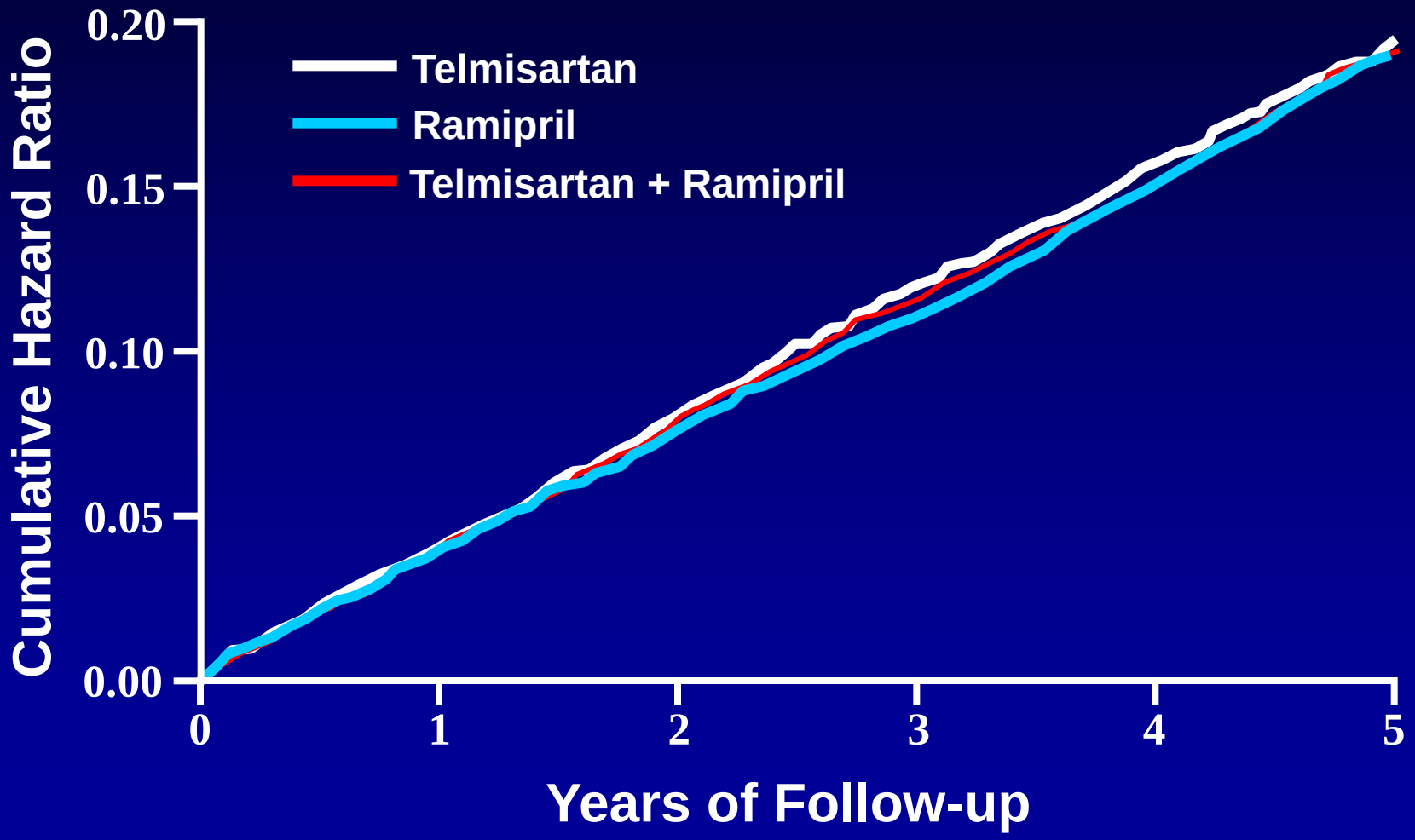
Follow-up of 3.5 to 5.5 years

Primary Outcomes	Composite of CV death, non-fatal MI, non-fatal stroke or hospitalization for congestive heart failure
Secondary Outcomes	Newly diagnosed congestive heart failure, revascularization procedures, DM, nephropathy, and atrial fibrillation
Other Outcomes	All cause mortality, Non-CV death, angina, TIAs, development of LVH, microvascular complications of DM, changes in BP and in ankle-arm BP ratio,malignancy

(Am Heart J 2004;148:52–61.)

ONTARGET

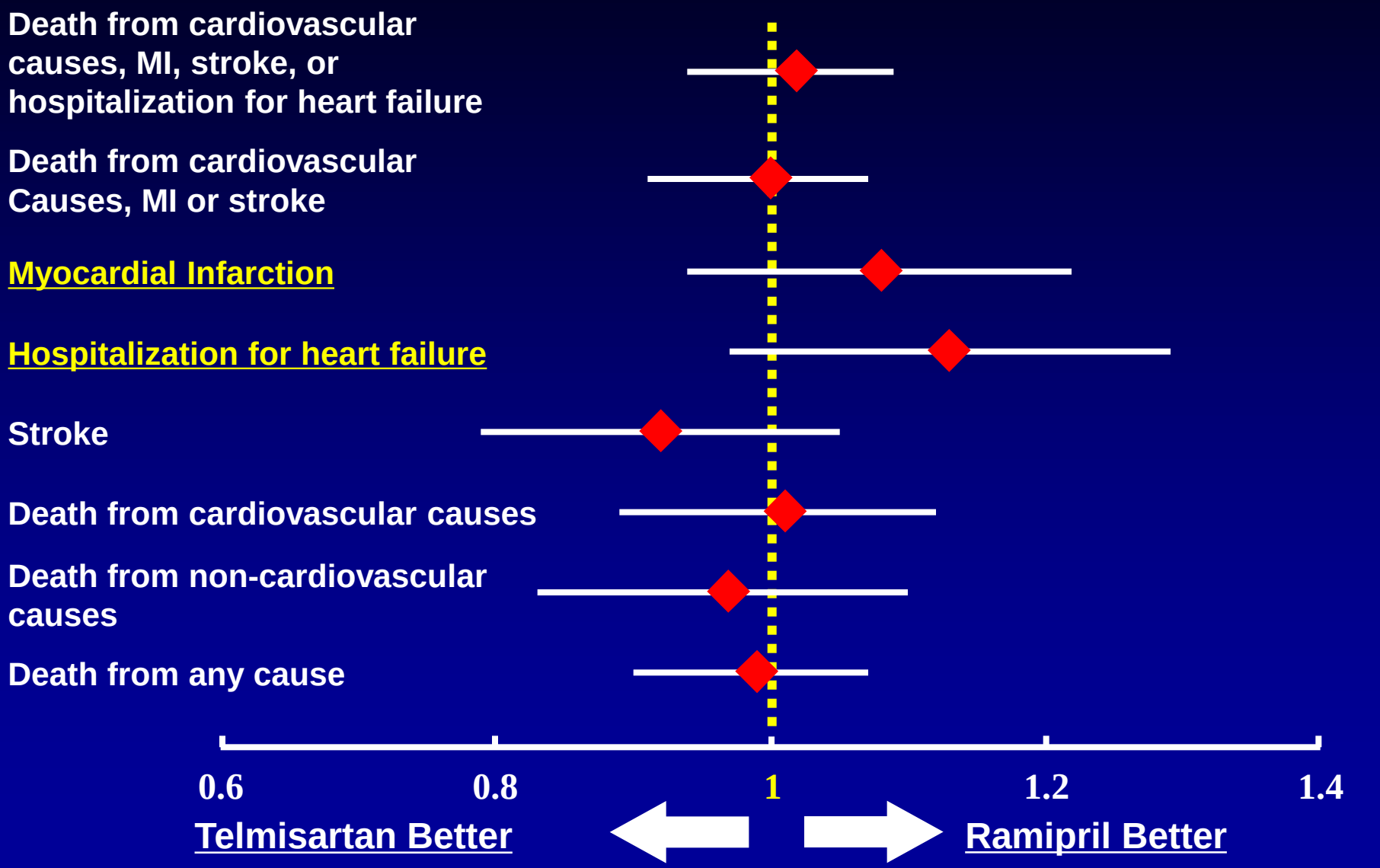
Kaplan-Meier Curves for the Primary Outcome in the Three Study Groups.



N Engl J Med 2008;358:1547-1549

ONTARGET

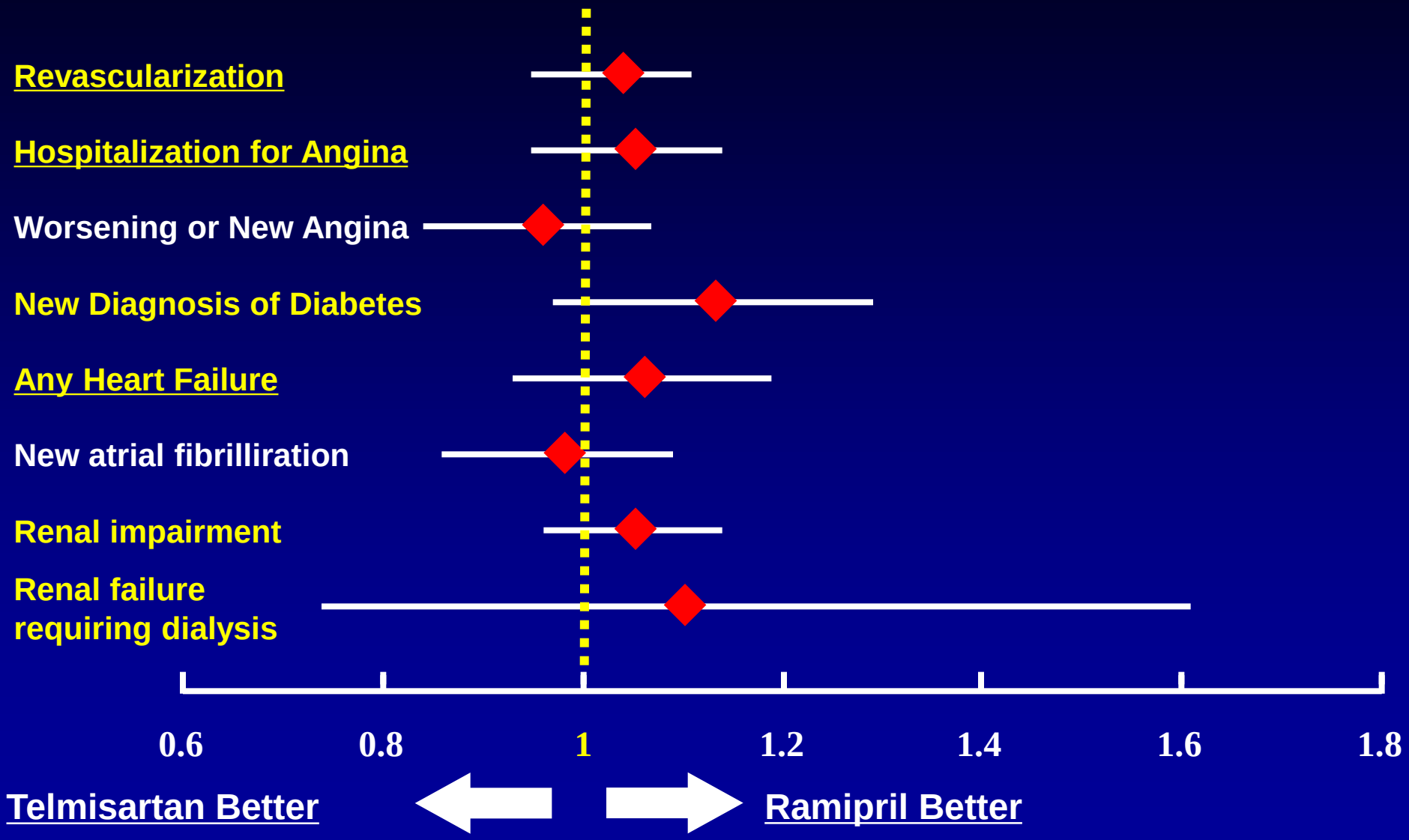
(Incidence of the Primary Outcome)



N Engl J Med 2008;358:1547-1549

ONTARGET

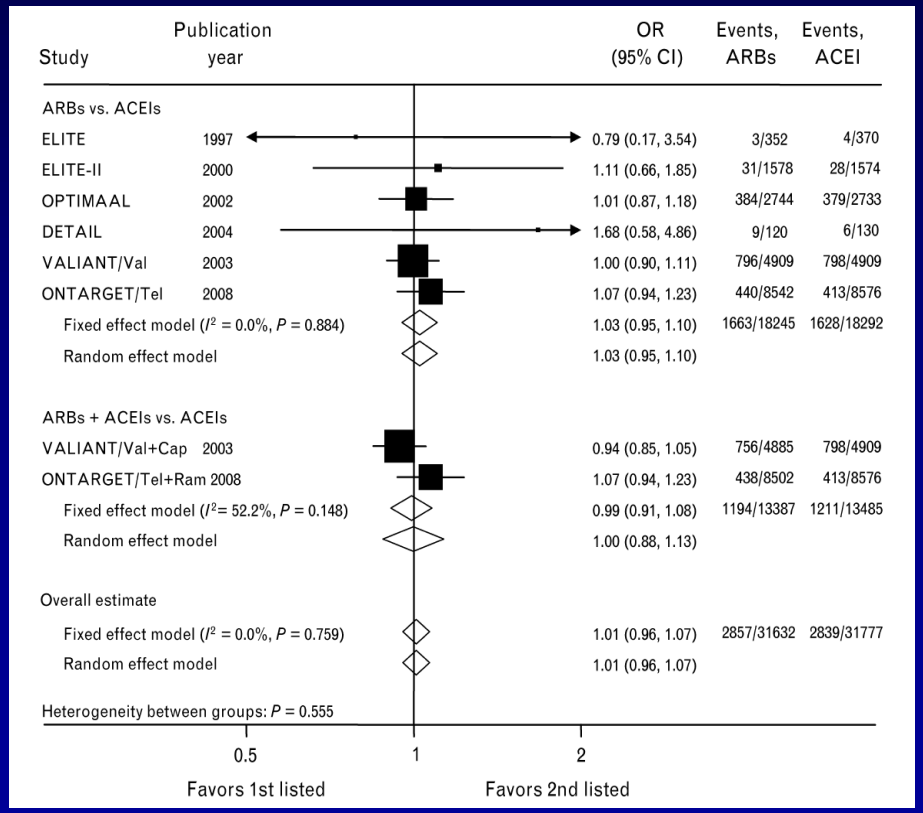
(Secondary and Other Outcome)



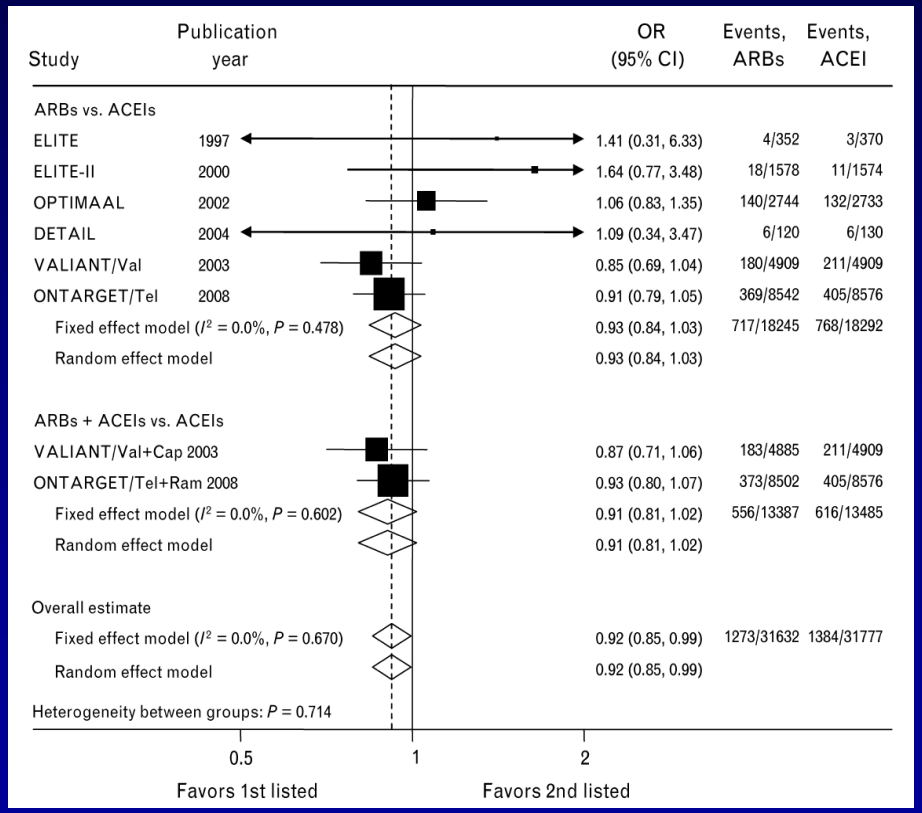
N Engl J Med 2008;358:1547-1549

ACEi 와 ARB 의 효과 비교

Myocardial infarction

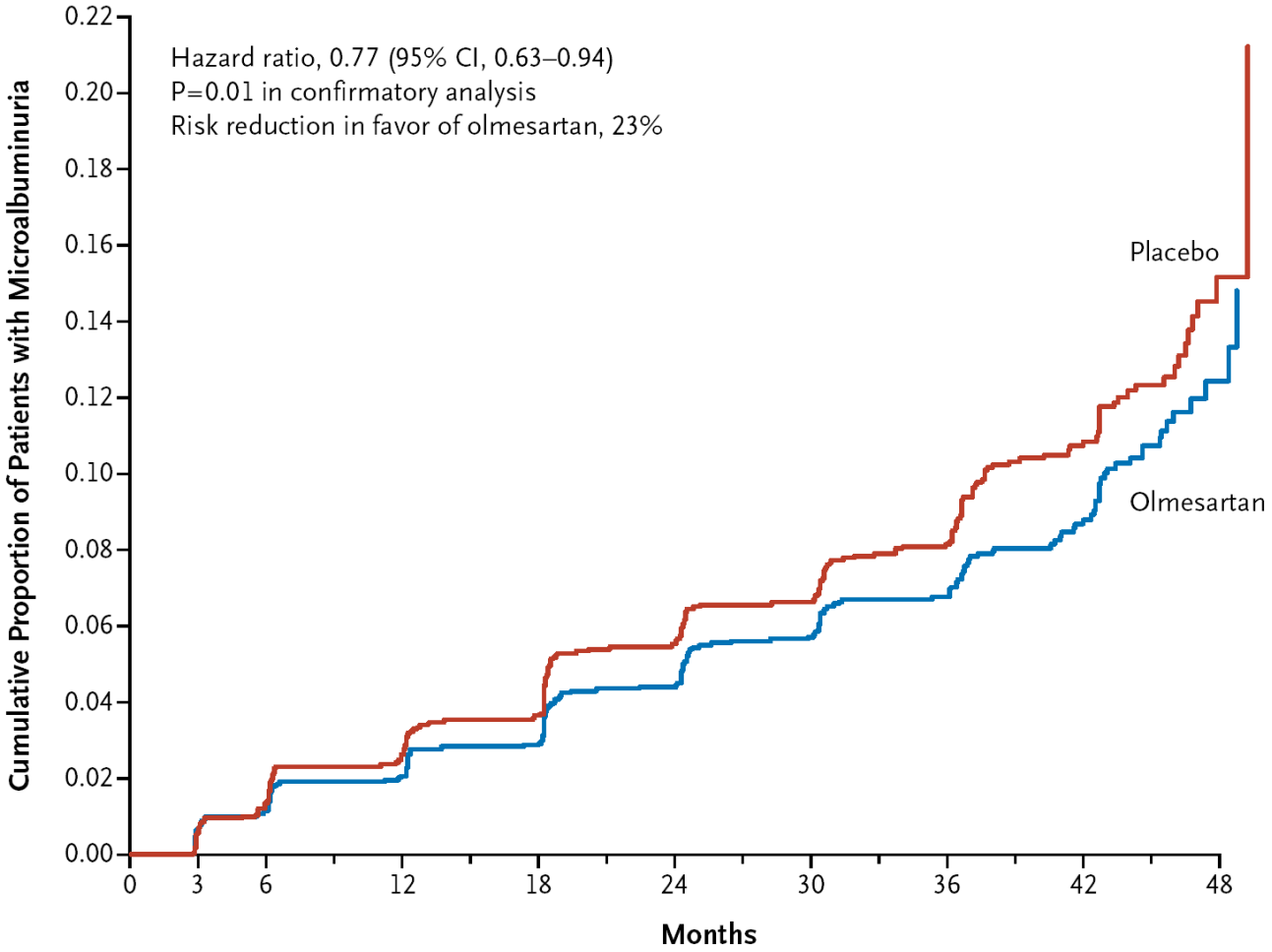


Stroke



Reboldi, *et al., J HT 2008*

ROADMAP STUDY



No. at Risk										
Olmesartan	2160	2097	2025	1923	1833	1727	1629	1325	754	67
Placebo	2139	2076	2004	1887	1787	1685	1592	1308	699	49

Haller et al, NEJM 2011

Return of ARB-MI paradox ?

End Point	Olmesartan (N = 2232)	Placebo (N = 2215)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)			
Composite of cardiovascular complications or death from cardiovascular causes	96 (4.3)	94 (4.2)	1.00 (0.75–1.33)	0.99
Composite of death from any cause	26 (1.2)	15 (0.7)	1.70 (0.90–3.22)	0.10
Death from cardiovascular causes	15 (0.7)	3 (0.1)		
Death not related to cardiovascular causes	8 (0.4)	10 (0.5)		
Death from unknown cause	3 (0.1)	2 (0.1)		
Composite of death from cardiovascular causes	15 (0.7)	3 (0.1)	4.94 (1.43–17.06)	0.01
Sudden cardiac death	7 (0.3)	1 (<0.1)		
Death due to fatal myocardial infarction	5 (0.2)	0		
Evidence of recent myocardial infarction on autopsy	0	0		
Death due to congestive heart failure	0	0		
Death during or after percutaneous transluminal coronary angioplasty or CABG	1 (<0.1)	0		
Death due to fatal stroke	2 (0.1)	2 (0.1)		

Haller et al, NEJM 2011

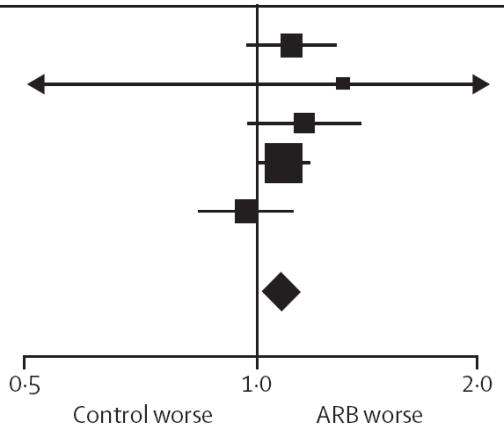
Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials

Ilke Sipahi, Sara M Debanne, Douglas Y Rowland, Daniel I Simon, James C Fang

A

	ARB	Control	Risk ratio (95% CI) for cancer occurrence	*Z* value	p value
LIFE[4,30]	358/4605 (7·8%)	320/4588 (7·0%)	1·12 (0·96–1·29)	1·465	0·143
TROPHY[6]	4/396 (1%)	3/391 (0·8%)	1·32 (0·30–5·84)	0·362	0·718
TRANSCEND[7,29]	236/2954 (8·0%)	204/2972 (6·9%)	1·16 (0·97–1·39)	1·650	0·099
ONTARGET[8,29]	1586/17 044 (9·3%)	735/8576 (8·6%)	1·09 (0·10–1·18)	1·931	0·054
PROFESS[9,29]	326/10 016 (3·3%)	340/10 048 (3·4%)	0·96 (0·83–1·12)	−0·510	0·610
Meta-analysis	**2510/35 015 (7·2%)**	**1602/26 575 (6·0%)**	**1·08 (1·01–1·15)**	**2·399**	**0·016**

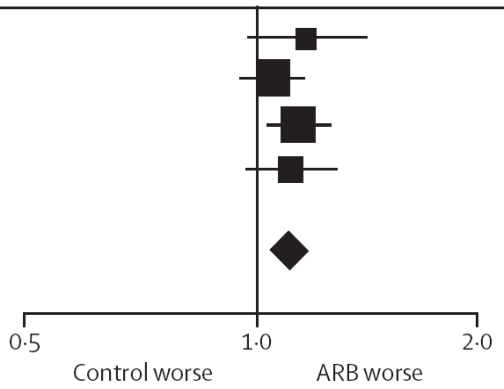
I^2=0%, fixed-effect model



B

	Risk ratio (95% CI) for cancer occurrence	*Z* value	p value
TRANSCEND[7,29]	1·17 (0·97–1·41)	1·645	0·100
ONTARGET[8,29] (telmisartan *vs* ramipril)	1·05 (0·95–1·16)	0·933	0·351
ONTARGET[8,29] (telmisartan+ramipril *vs* ramipril)	1·14 (1·03–1·26)	2·548	0·011
LIFE[4,30]	1·12 (0·96–1·29)	1·465	0·143
Meta-analysis	**1·11 (1·04–1·18)**	**3·244**	**0·001**

I^2=0%, fixed-effect model



Sipahi**, et al., **Lancet Oncol 2010

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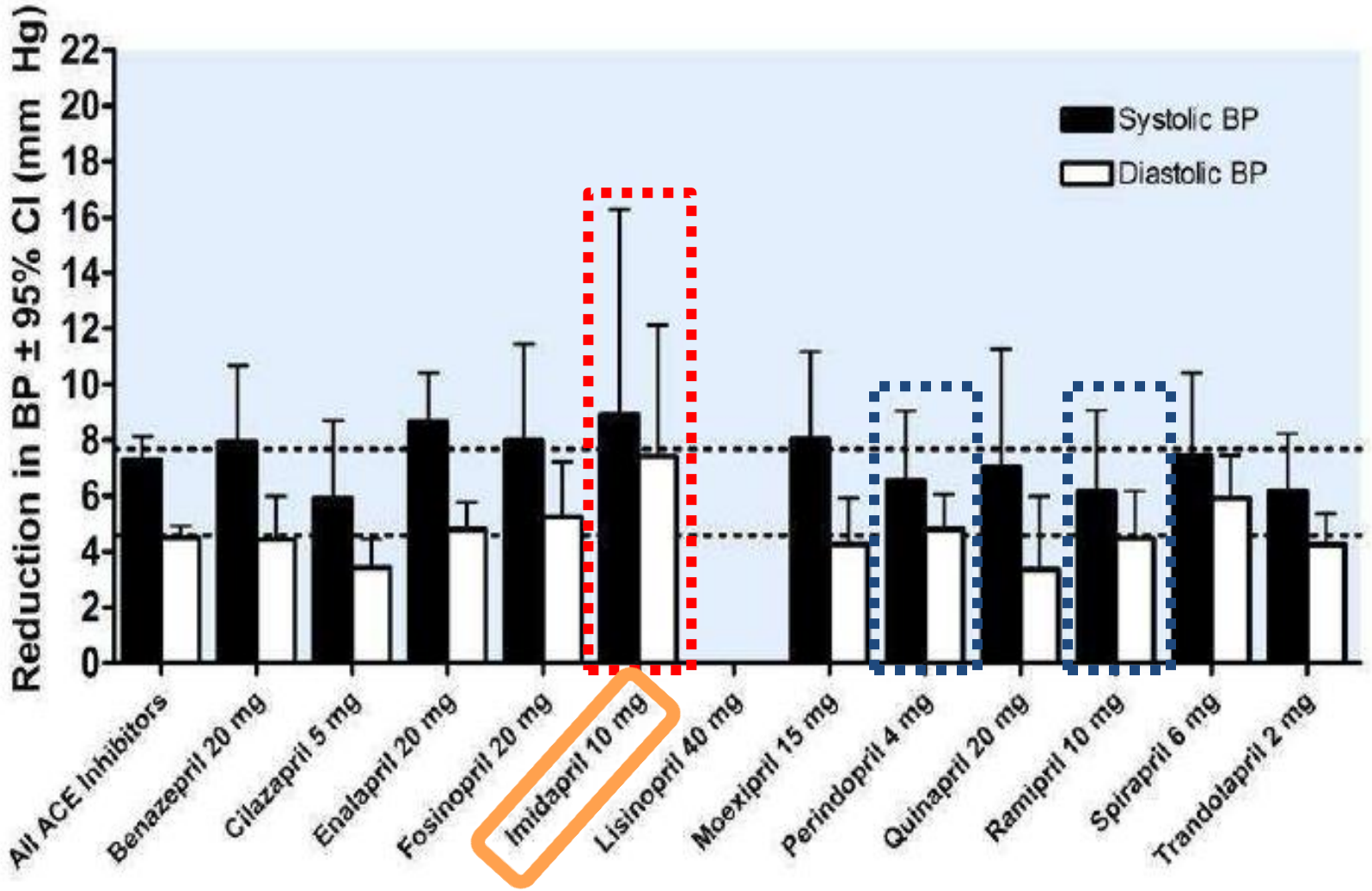
Blood pressure lowering efficacy of ACE inhibitors for primary hypertension (Cochrane Review)



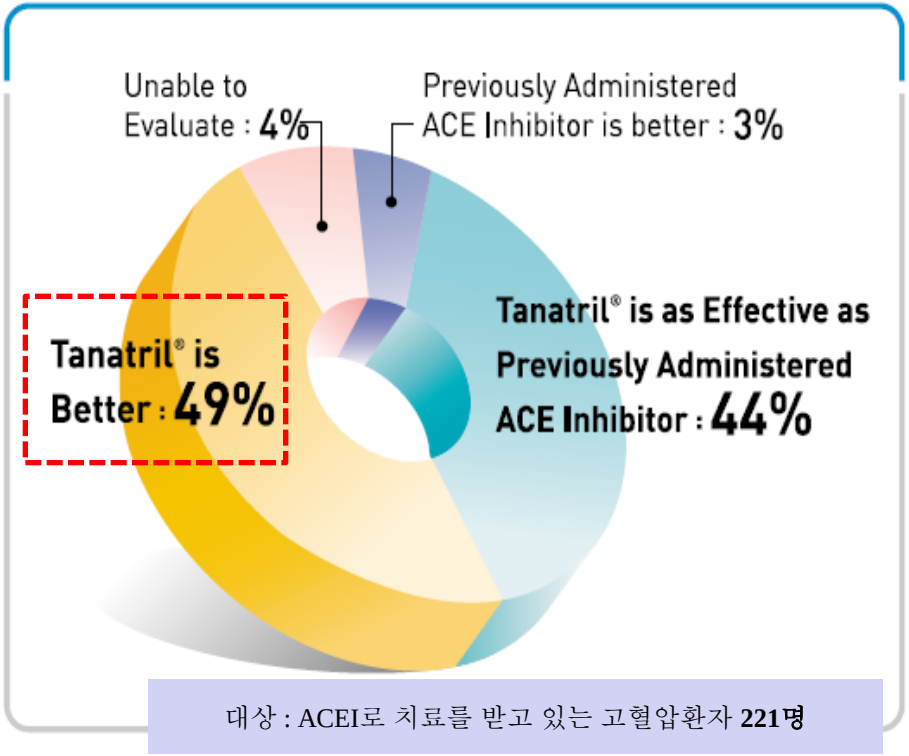
Cochrane Database of Systematic Reviews, Issue 1, 2009

Well-controlled BP with once a day administration

Drug	Dose range(mg)	T/P ratio (%)
Tanatril®	**5 ~ 20**	**63 ~ 84**
Fosinopril	20	64
Ramipril	5 ~ 10	50 ~ 63
Enalapril	5 ~ 20	40 ~ 64
Lisinopril	10 ~ 80	30 ~ 70
Perindopril	4 ~ 8	35
Captopril	25 ~ 100	25
Moexipril	7.5 ~ 15	0 ~ 9

Song JC et al.;Clin . Pharmacokinet 41, 207(2002)

49% patients showed better BP Control than other ACEIs

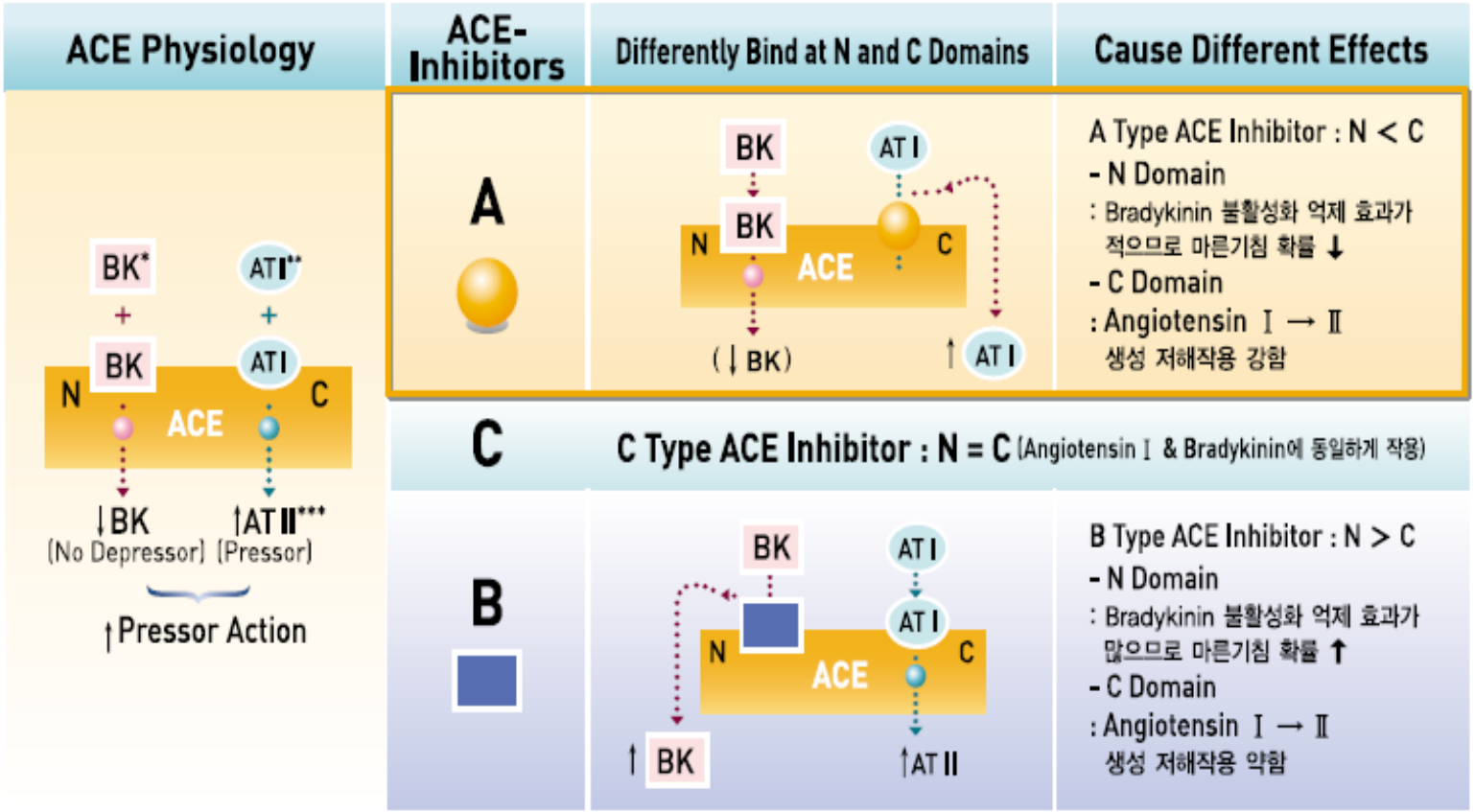


대상 : ACEI로 치료를 받고 있는 고혈압환자 **221**명

T. Sawayama Jpn J. Clin. Exp. Med., 76, 619(1999)

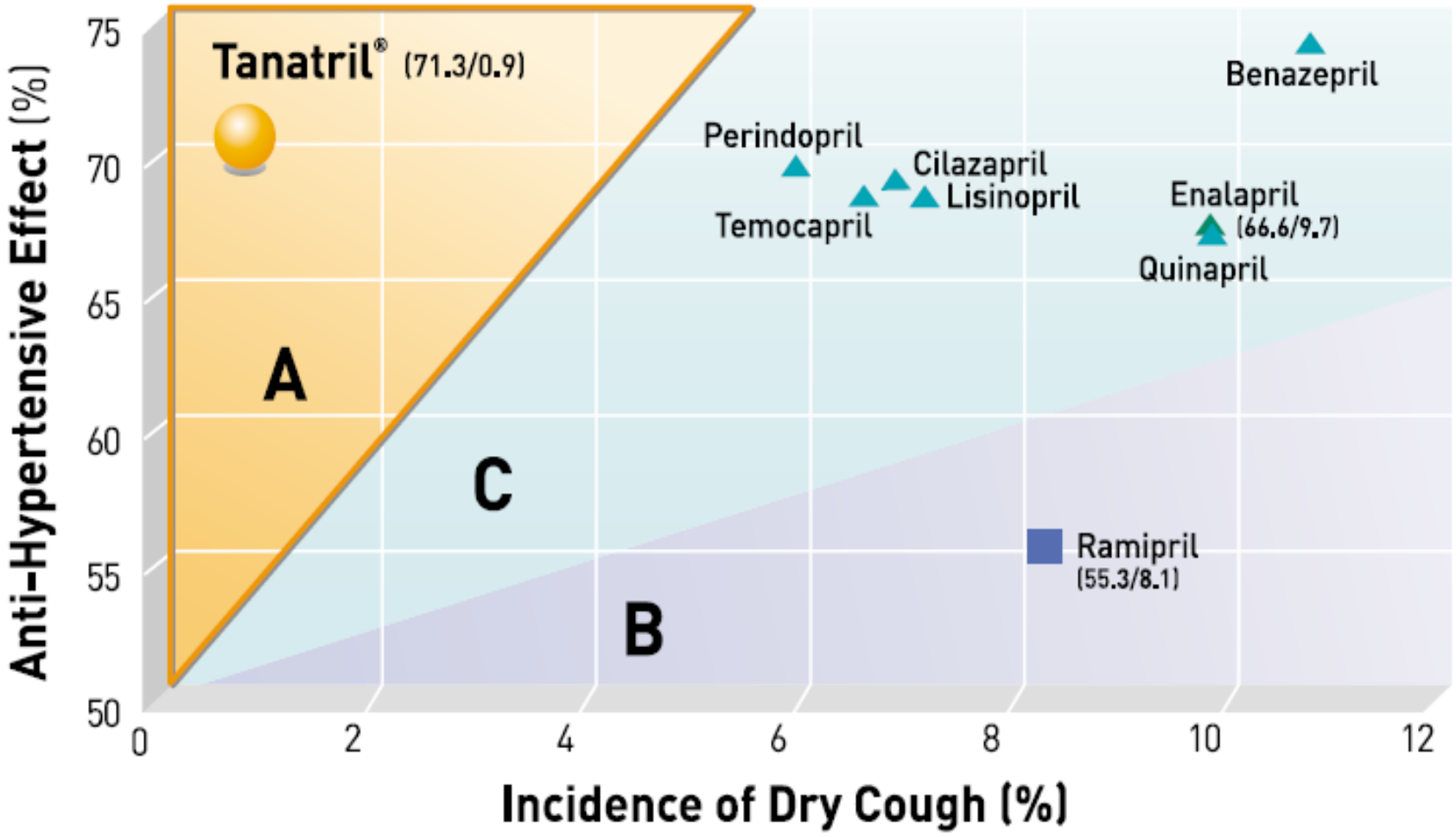
High Anti-Hypertensive Effect with Low Incidence of Dry Cough

Hypothetic ABC Classification of ACE-Inhibitors



*BK : Bradykinin ** AT I : Angiotensin I ***AT II : Angiotensin II

Imidapril : Efficacy & Safety



M. Sasaguri et al.; Hypertens. Res., 17, 253(1994)

Imidapril : Low Incidence of Dry Cough

Imidapril은 현존하는 국내 ACEI 중에 가장 낮은 마른기침 발생율을 보입니다.

Dry Cough of ACEI in KOREA

	Rho[1)] 1994	Yoo[2)] 1997	Park[3)] 1998	Lee[4)] 1998
Enalapril	33.8% (23/68)			
Fosinopril			16.3% (8/49)	
Ramipril		15.2% (5/33)		
Delapril		9.1% (3/33)		
Imidapril		**7.8%** (16/204)		**8.7%** (2/23)
Losartan			**4.3%** (2/47)	

1) Roh SI et al. Korean J Med 1994;47(1):66-71.
2) Yoo WS, et al. The Korean Society of Hypertension 1997;3(1):47-52.
3) Park DG,et al. Korean circulation J 1998;28(1):15-26.
4) Lee SB et al. Korean Circulation J 1998;28(7):1154-1160

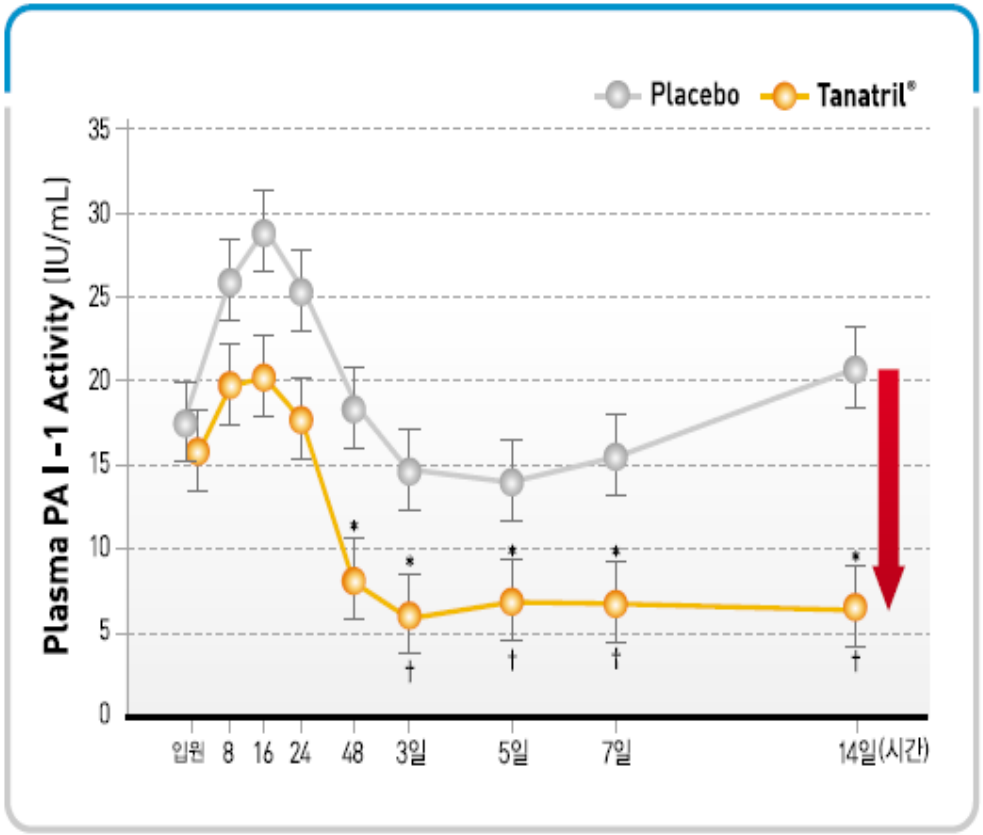
Imidapril : Anti-thrombotic effect in MI patient

Decreasing Activation of PAI-1

Imidapril 은 PAI-1의 활성화를 억제함으로써, t-PA의 생성을 촉진하여 심근경색 환자의 혈전 생성을 억제합니다.

대상환자	고혈압 병력을 가지고 있는 급성 심근경색증 환자 40명
시험방법	급성 심근경색 발병 후 12시간 내의 환자들에게 2주간 Tanatril (n=20), Placebo (n=20) 투약 (혈장 내 Plasminogen Activator Inhibitor (PAI)와 Serum ACE 수치 검사 실시를 위해 시행됨)

*p< 0.01 vs Placebo †p< 0.01 vs 입원 시 *t*-test

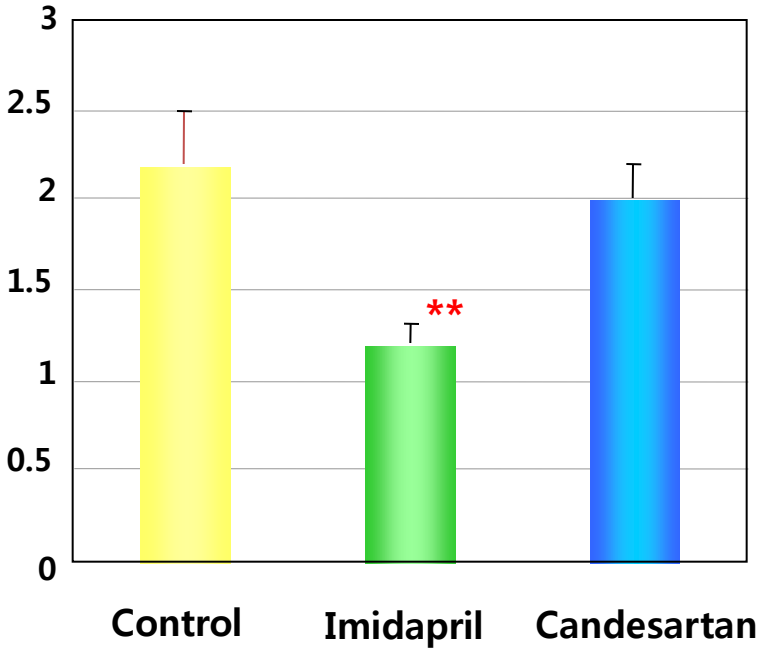


Reference. Oshima S et al : Am Heart J., 134; 961-6 (1997)

Imidapril : PAI-1 activity & Fibrinolysis

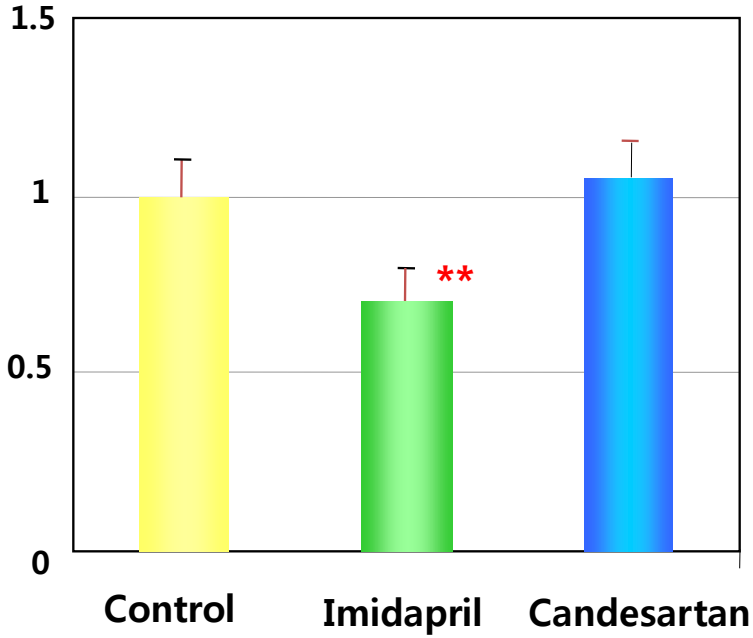
Decreasing Activation of PAI-1

Dry weight of thrombus (mg)



Mean±S.E. ** : p<0.01

Aortic PAI-1 activity (ratio)



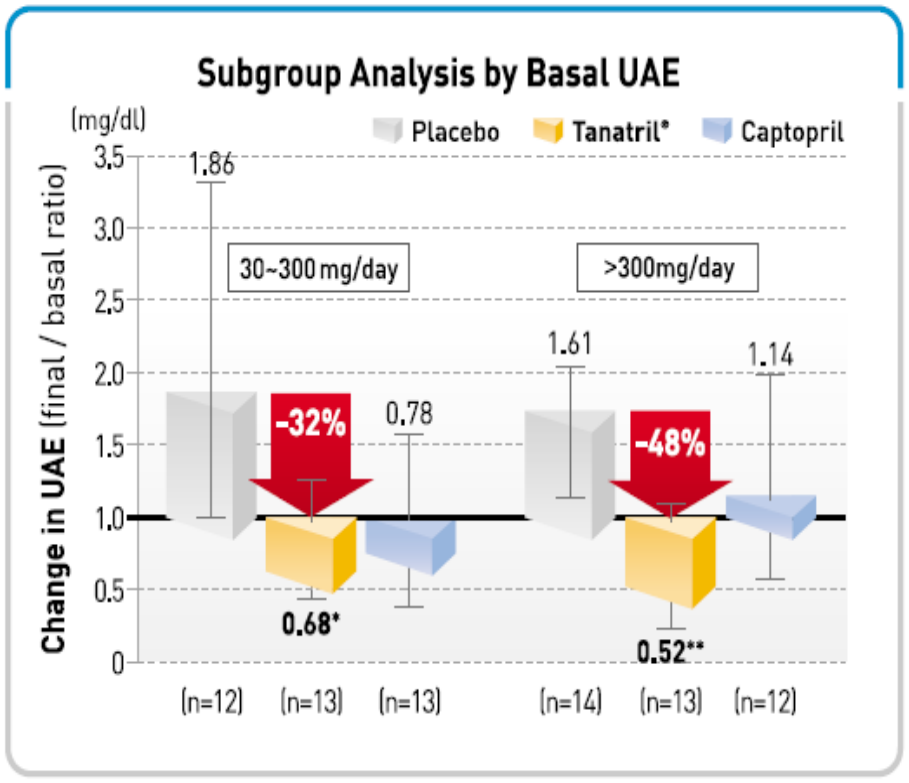
Animal : Spontaneously hypertensive rats (SHRs), n=9-13

Methods : A thrombus was induced in the abdominal aorta by electrical stimulation. Imidapril or Candesartan were administered before the current application. The thrombus was removed, and its dry weight was measured. In addition, aortic PAI-1 protein and PAI-1 activity were measured.

Mitus-T,et al.,Biol Pharm Bull 22 863 (1999)

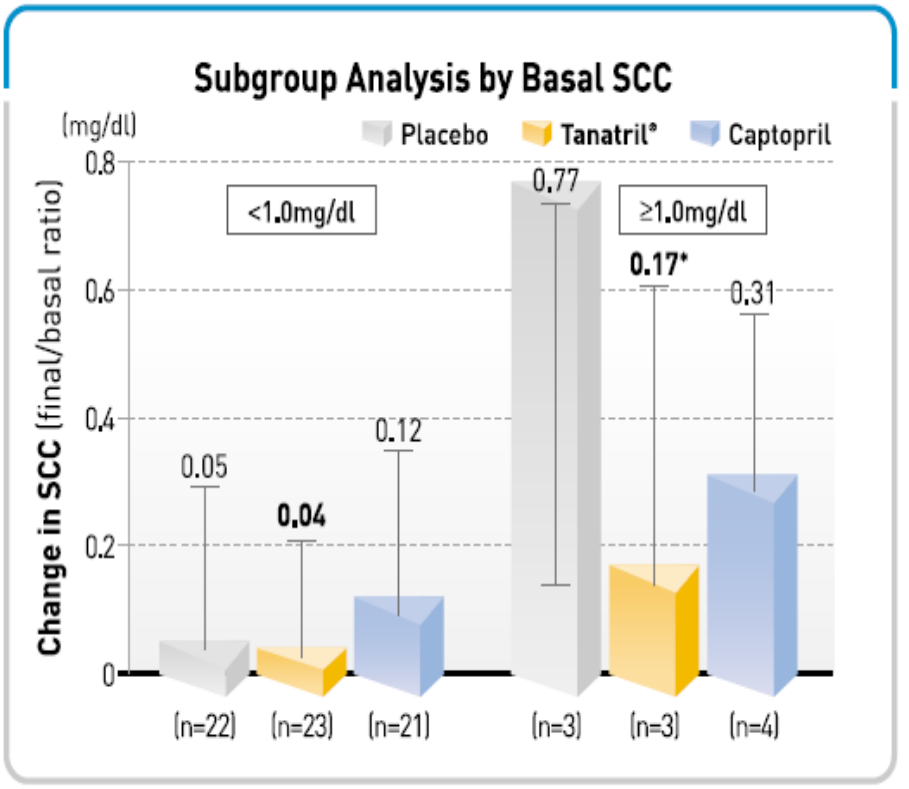
Imidapril : Effects on Diabetic Nephropathy (JAPAN-IDDM)

Change in urinary albumin excretion



Reference. S.Katayama, R. Kikkawa, S. Isogai et al.: Diabetes Res Clin Pract., 55, 113 (2002)

Change in serum creatinine



Reference. S.Katayama, R. Kikkawa, S. Isogai et al.: Diabetes Res Clin Pract., 55, 113 (2002)

CONCLUSION

1. ***Benefits of RAS inhibitor***

   → ***RAS inhibitors reduce more risk of hypertension with complications than other BP lowering Agent.***

2. ***Can ARBs replace ACEI ?***

   → ***ARB didn't show significant reduction in the risk of MI & CHD comparing with ACEI.***

3. ***Imidapril : New Generation ACEI***

   → ***Better antihypertensive effect with lower dry cough than any other ACEI.***

   → ***Reducing risk of MI, CHF, and LVH in patients with CV disease***

Thank you for attention~!