Losartan의 항혈소판 효과

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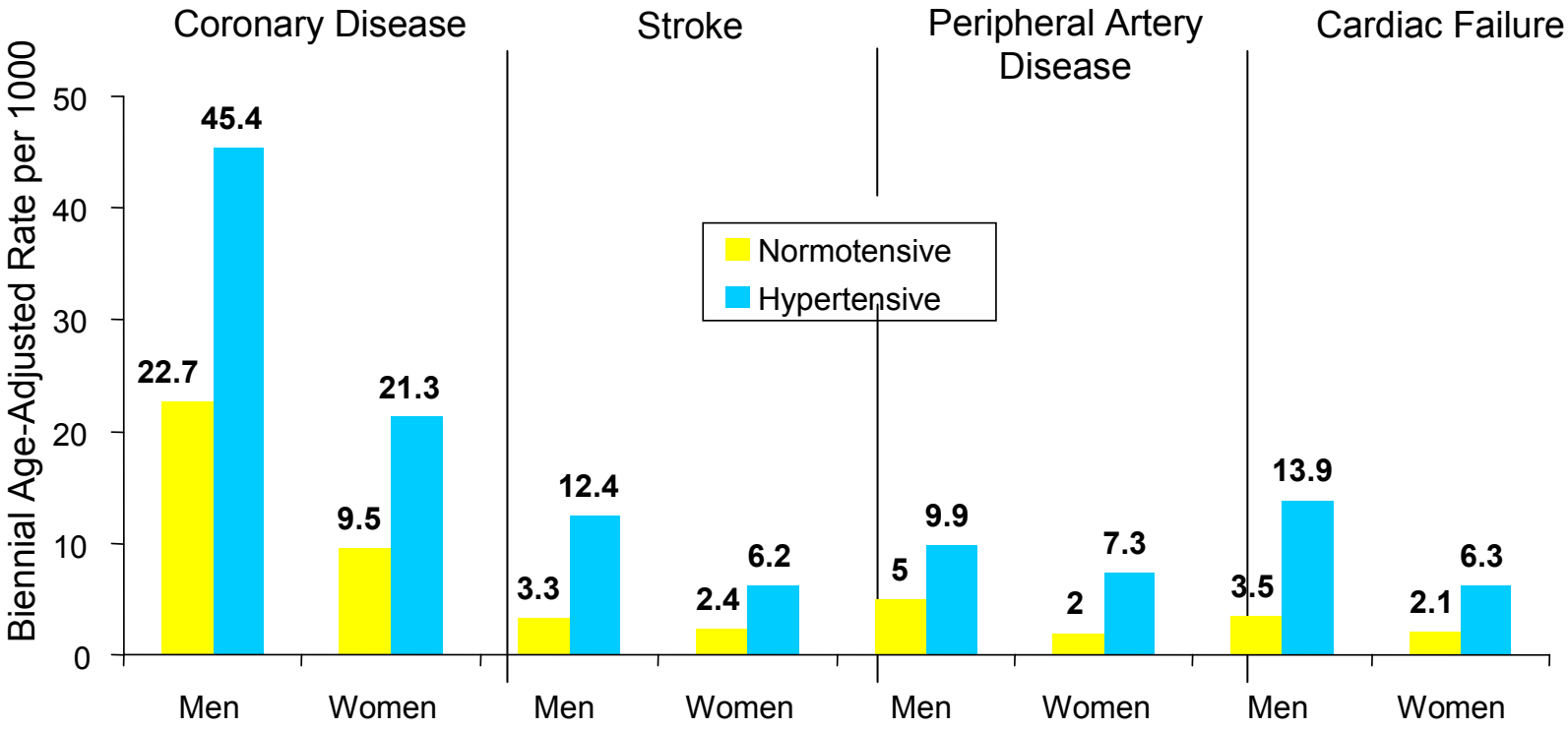
Hypertensive Patients Are at Increased Risk for Cardiovascular Events

Framingham Heart Study
- Risk of Cardiovascular Events by Hypertensive Status in Patients Aged 35-64 Years; 36-Year F-U



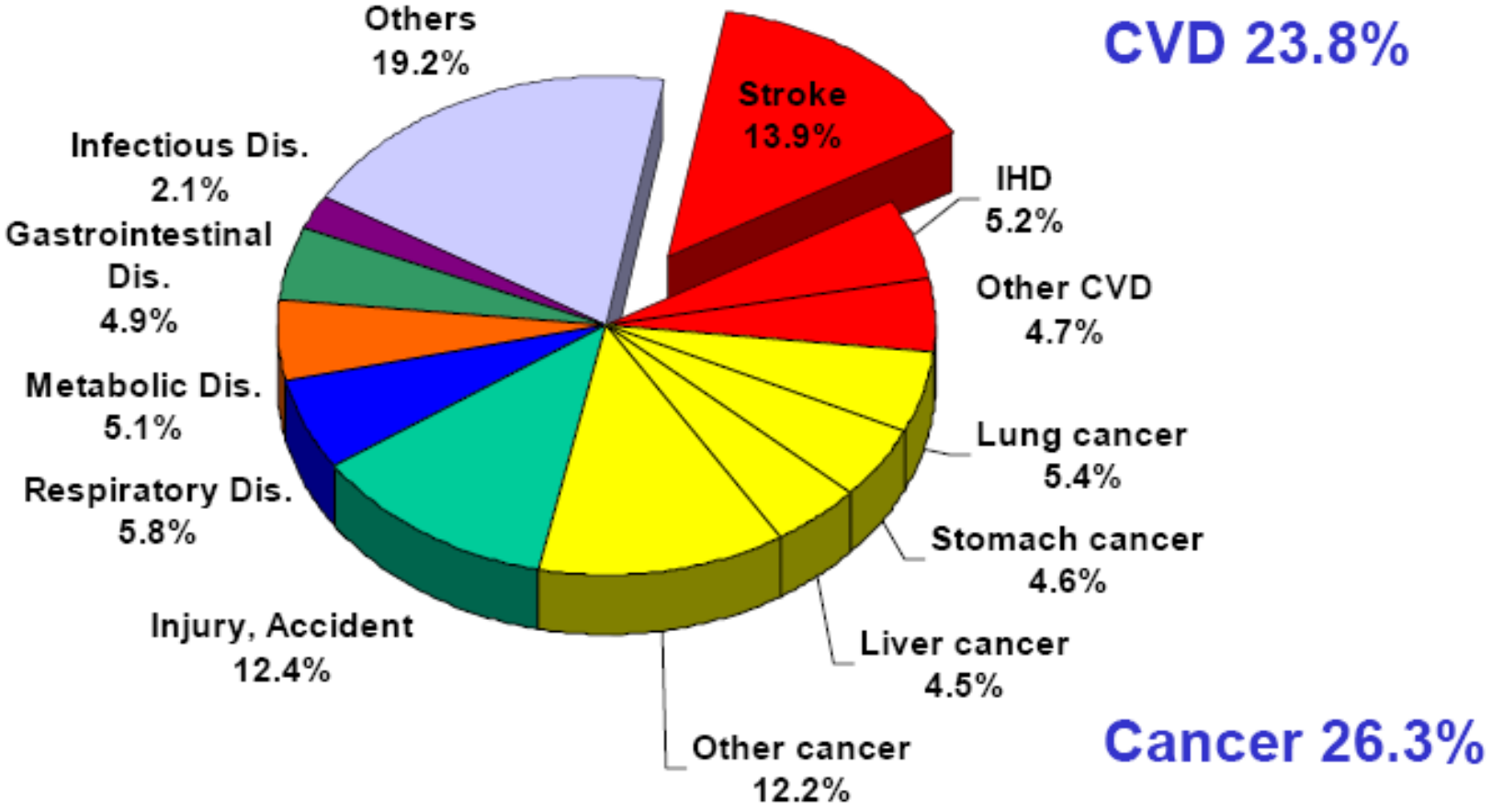
Risk Ratio	2.0	2.2	3.8	2.6	2.0	3.7	4.0	3.0
Excess Risk	22.7	11.8	9.1	3.8	4.9	5.3	10.4	4.2

Kannel WB *JAMA* 1996;275(24):1571-1576.

Benefits of Lowering BP

	Average Percent Reduction
Stroke incidence	35–40%
Myocardial infarction	20–25%
Heart failure	50%

Causes of deaths in Korea, 2004

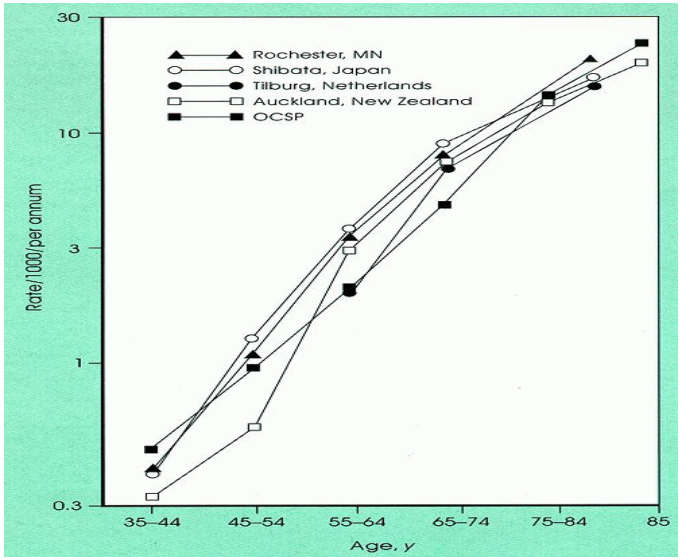


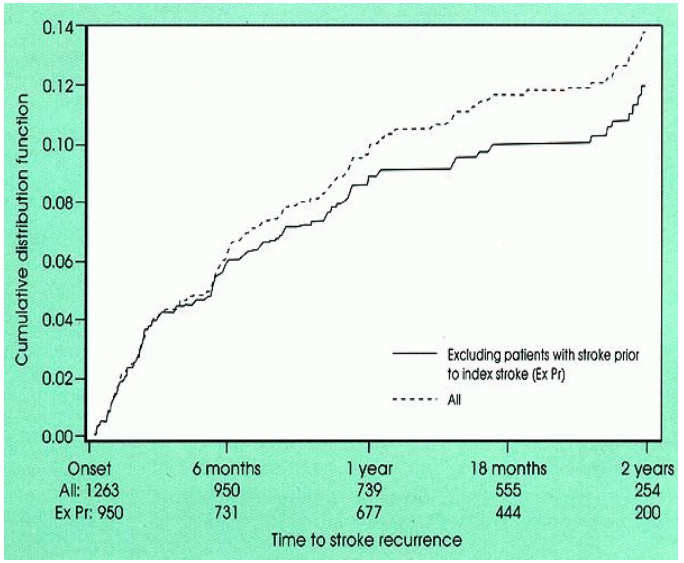
Data: National Statistical Office, Korea

뇌졸중의 역학적 특성

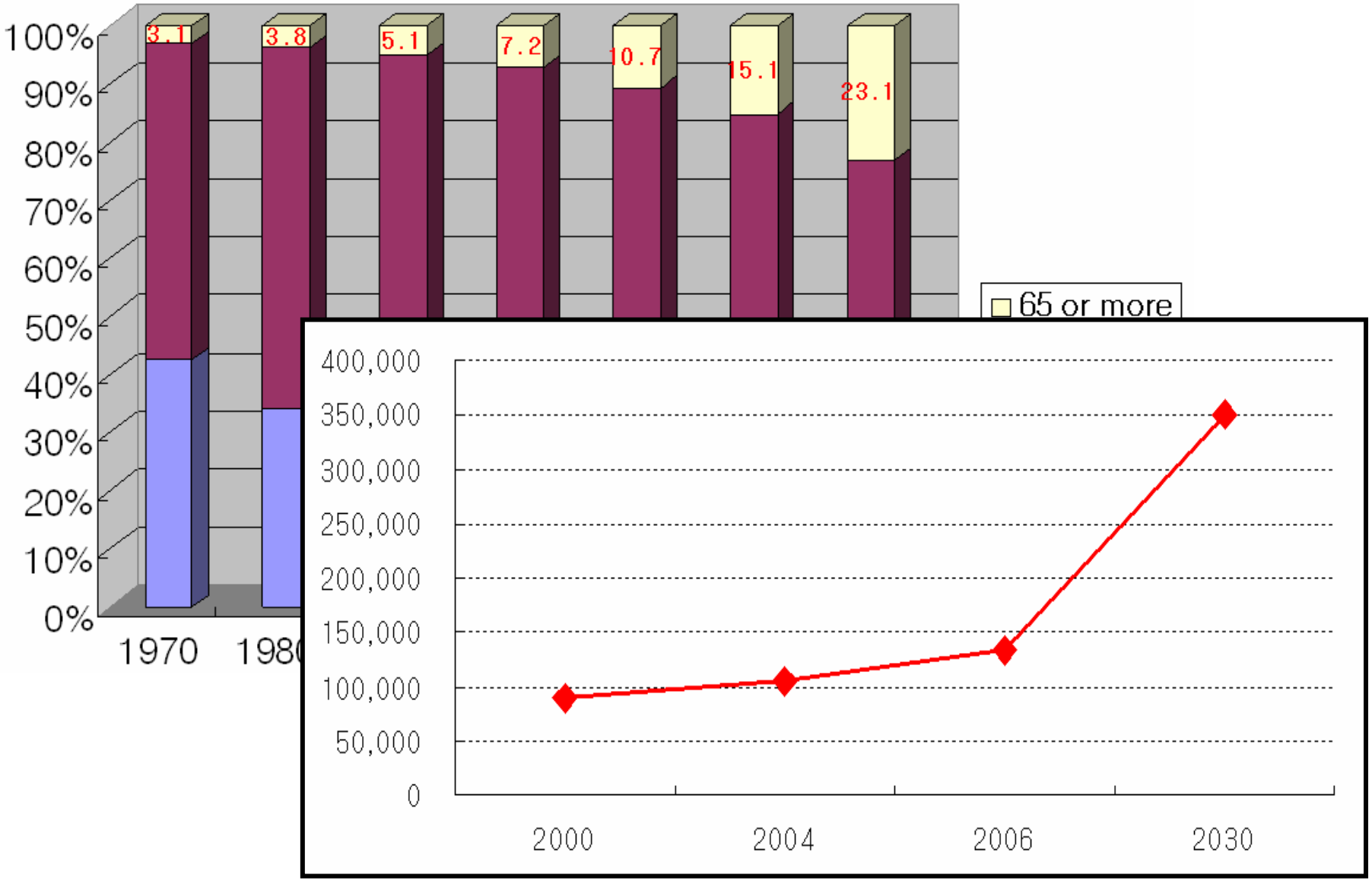
- 노령(>65세) 에서 흔히 발병
  - 100-300/100,000 per year
- 높은 사망률 (국내 2위)
  - 치명율 8-20% (<30 days)
- 빈번한 후유장해
- 높은 재발 위험
  - 1st 30 days: 3-10%
  - Long-term: 4-14% / yr

* 심각한 부담 (가족, 사회, 국가)





노령화와 뇌졸중의 발병률 (추정)



주요 위험인자의 유병률과 위험도

Factor	Prevalence, %	Relative Risk
Hypertension	25-40	3-5
Elevated total cholesterol level (>240 mg/dL [6.21 mmol/L])	6-40	1.8-2.6
Smoking	25	1.5
Physical inactivity	25	2.7
Obesity	18	1.8-2.4
Asymptomatic carotid stenosis (>50%)	2-8	2
Alcohol consumption (>5 drinks/d)	2-5	1.6
Atrial fibrillation	1	5 (nonvalvular); 17 (valvular)

The **L**osartan **I**ntervention **F**or **E**ndpoint Reduction in Hypertension Study

A multicenter, multinational, double-blind, randomized, parallel study to investigate the effect of losartan, compared to atenolol, on the reduction of cardiovascular morbidity and mortality in hypertensive patients with left ventricular hypertrophy.

LIFE: Key Inclusion Criteria

- Age 55-80 years
- Elevated blood pressure
  - Systolic BP 160-200 mm Hg
    or
    Diastolic BP 95-115 mm Hg
- ECG LVH
  - Cornell Voltage Duration Product
    or
    Sokolow-Lyon Criterion

LIFE: Baseline Characteristics (I)

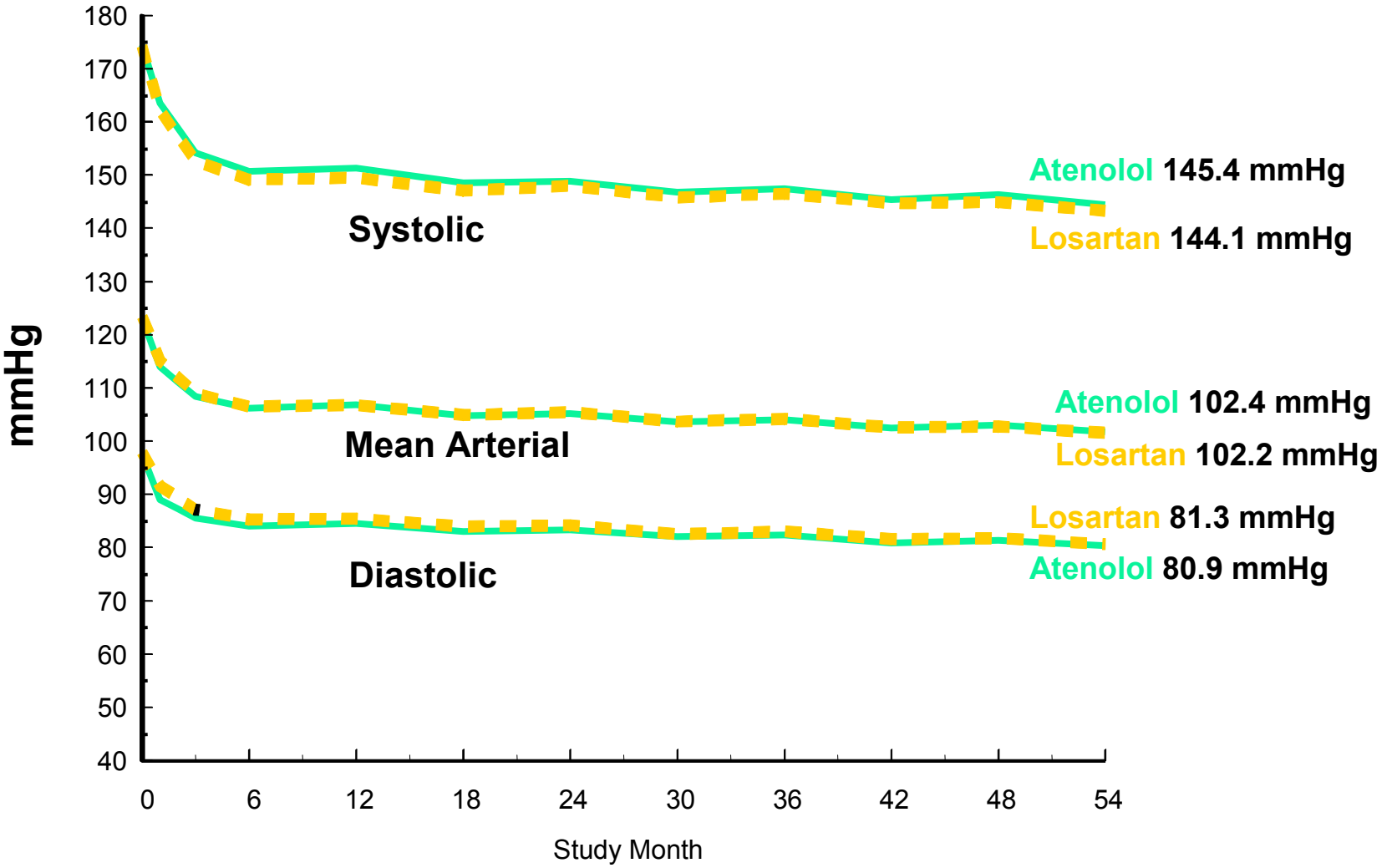
	Losartan (N=4605)	Atenolol (N=4588)
Age (mean), years	66.9	66.9
Gender, % female	54.0	54.0
Systolic BP, mm Hg	174.3	174.5
Diastolic BP, mm Hg	97.9	97.7
Pulse rate, bpm	73.9	73.7
BMI, kg/cm^2	28.0	28.0
Smokers, %	15.8	16.8

LIFE: Baseline Characteristics (II)

Medical History

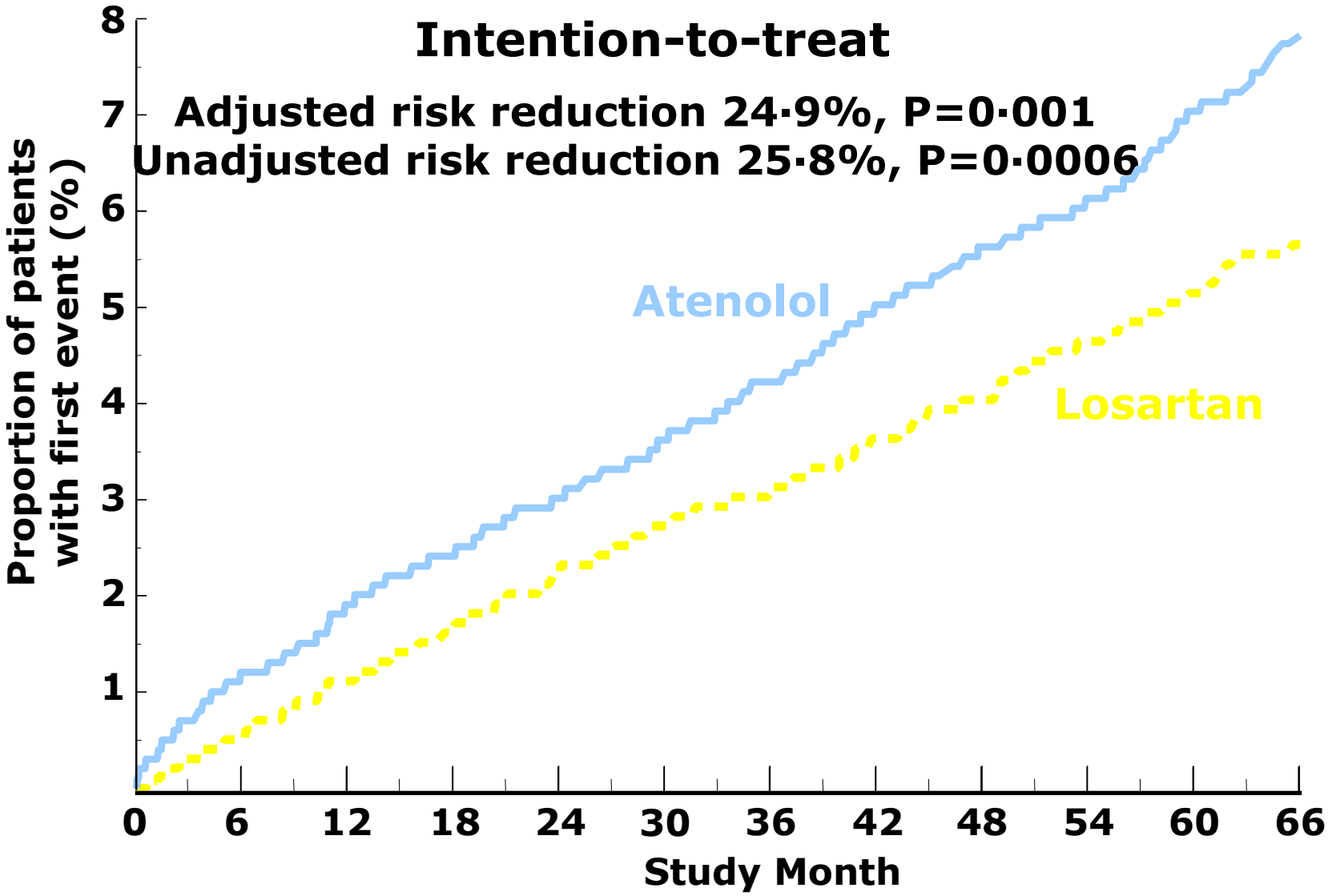
	Losartan % (N=4605)	Atenolol % (N=4588)
Diabetes mellitus	12.7	13.3
ISH (≥160 / <90 mm Hg)	14.3	14.5
Coronary heart disease	16.7	15.2
Myocardial infarction	6.7	5.7
Cerebrovascular disease	8.2	8.0
Stroke	4.1	4.6

LIFE: Comparable BP Reductions

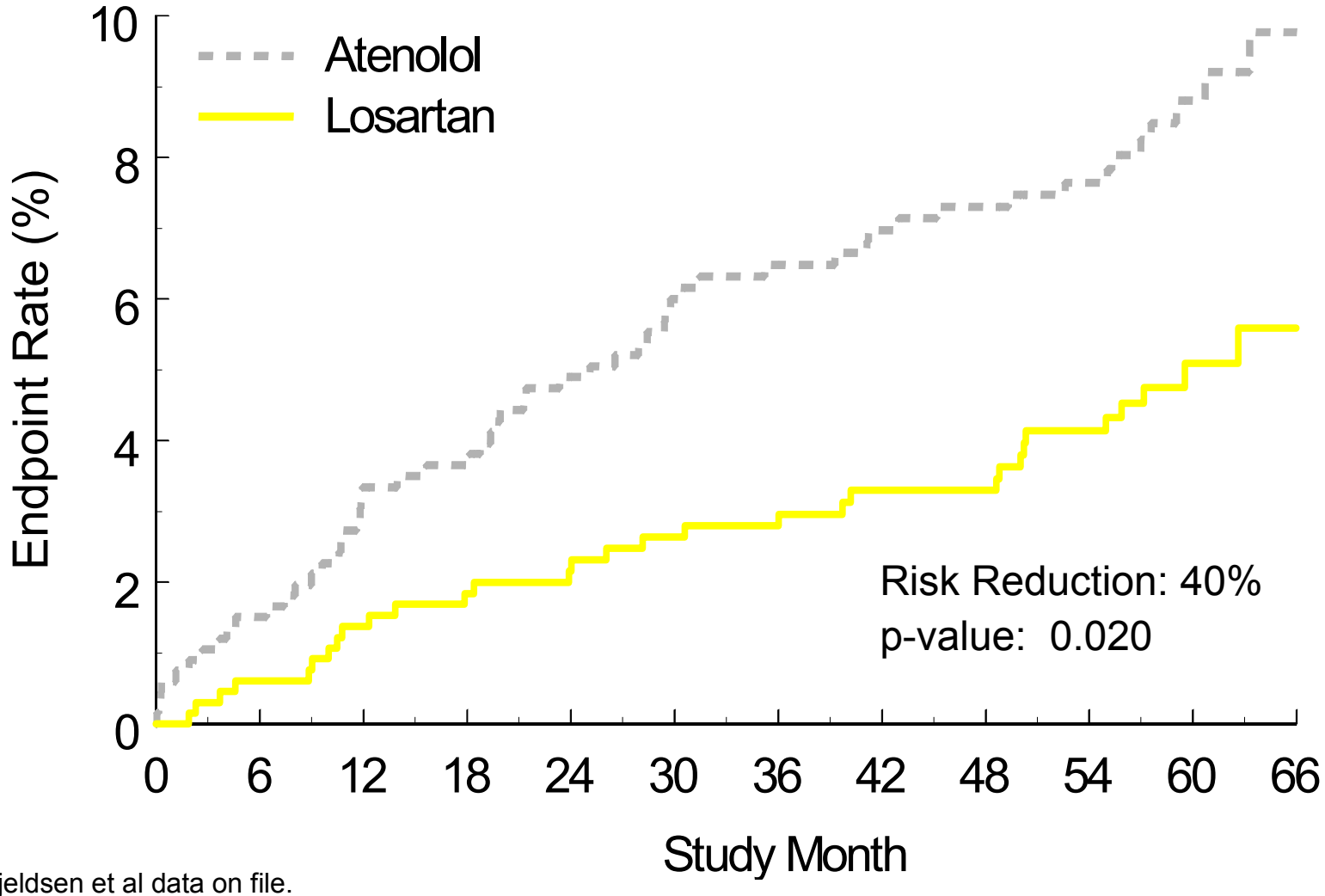


Dahlöf B et al *Lancet* 2002;359:995-1003.

Fatal and Non-Fatal Stroke

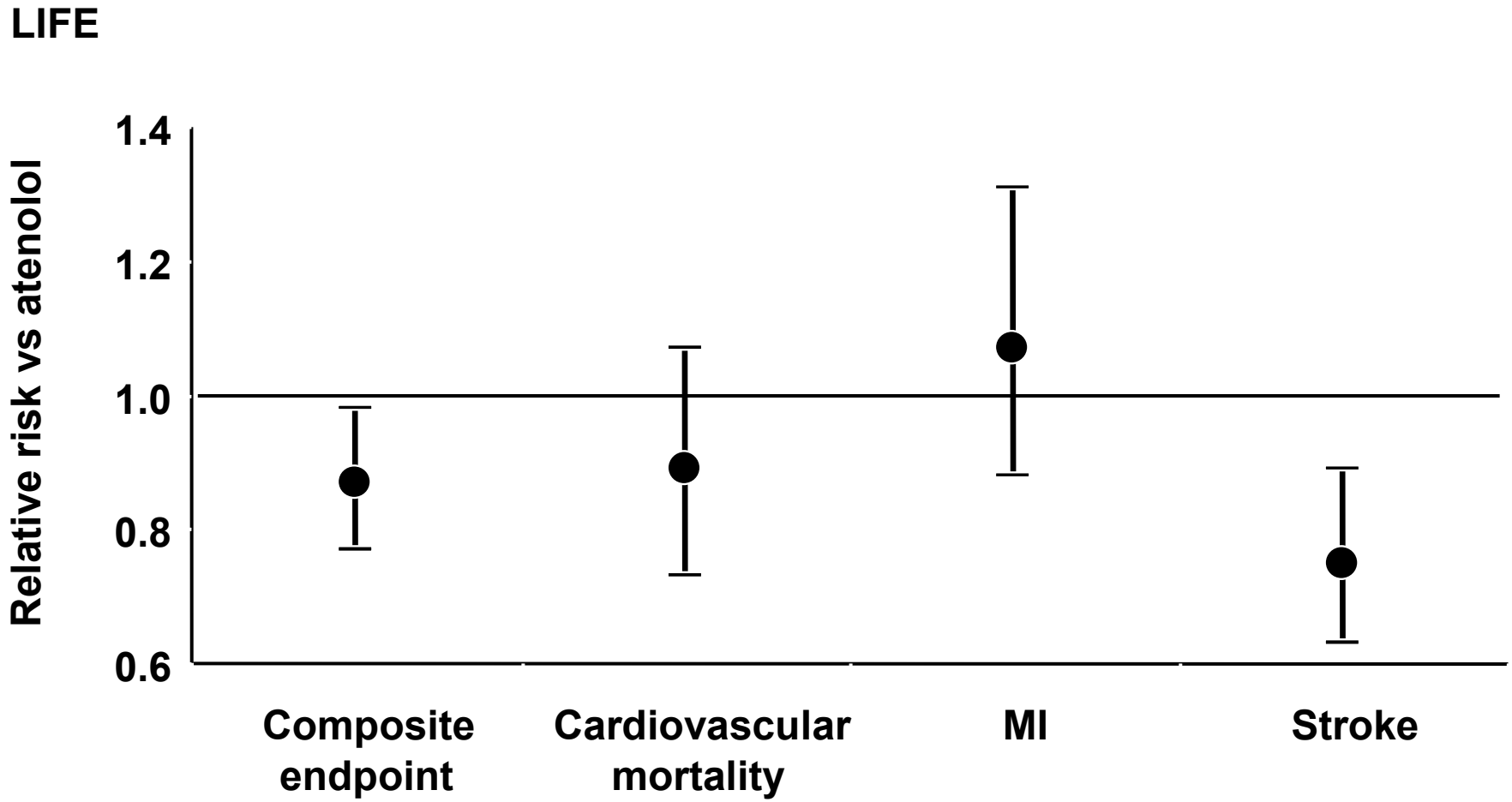


LIFE: ISH – Fatal/Nonfatal Stroke



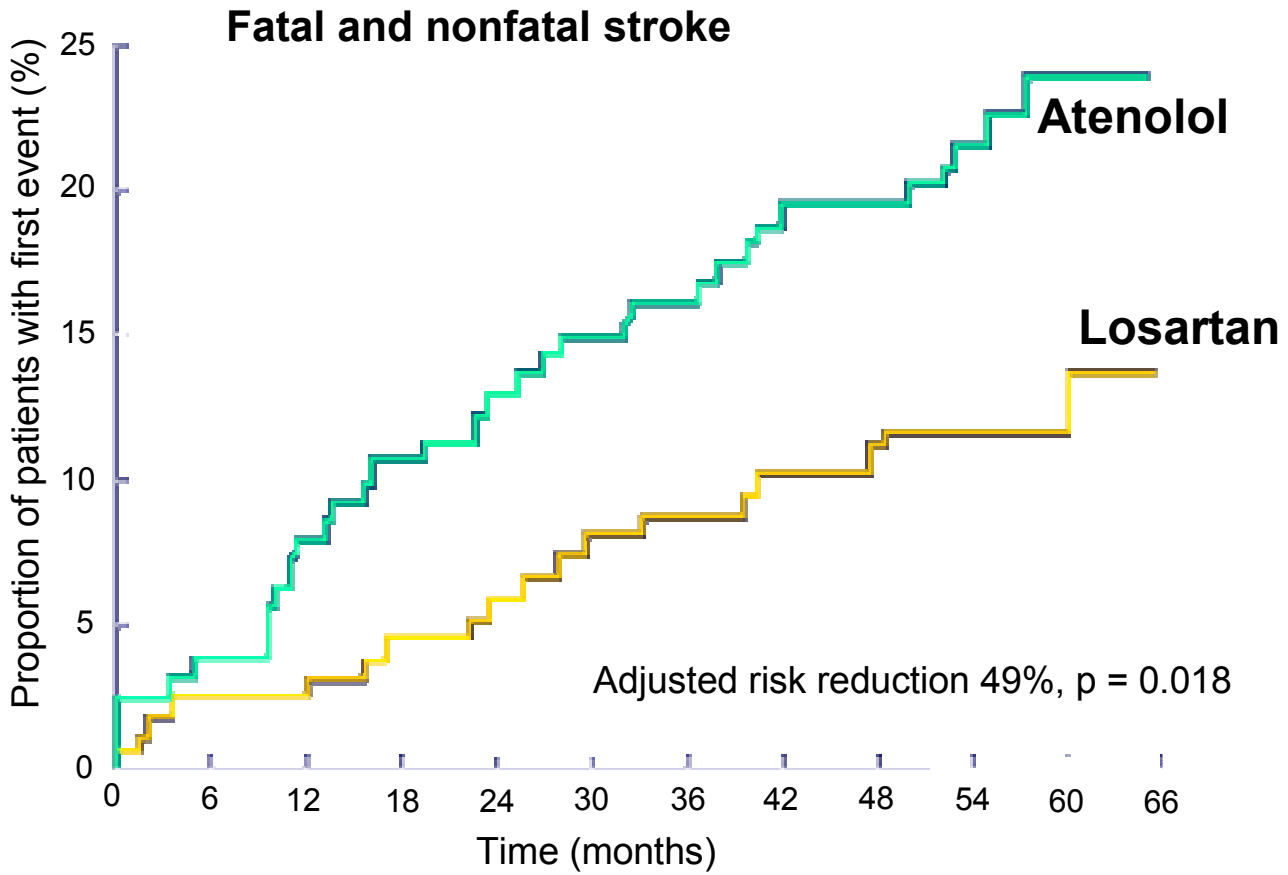
SE Kjeldsen et al data on file.

Cardiovascular effects of losartan primarily due to stroke reduction



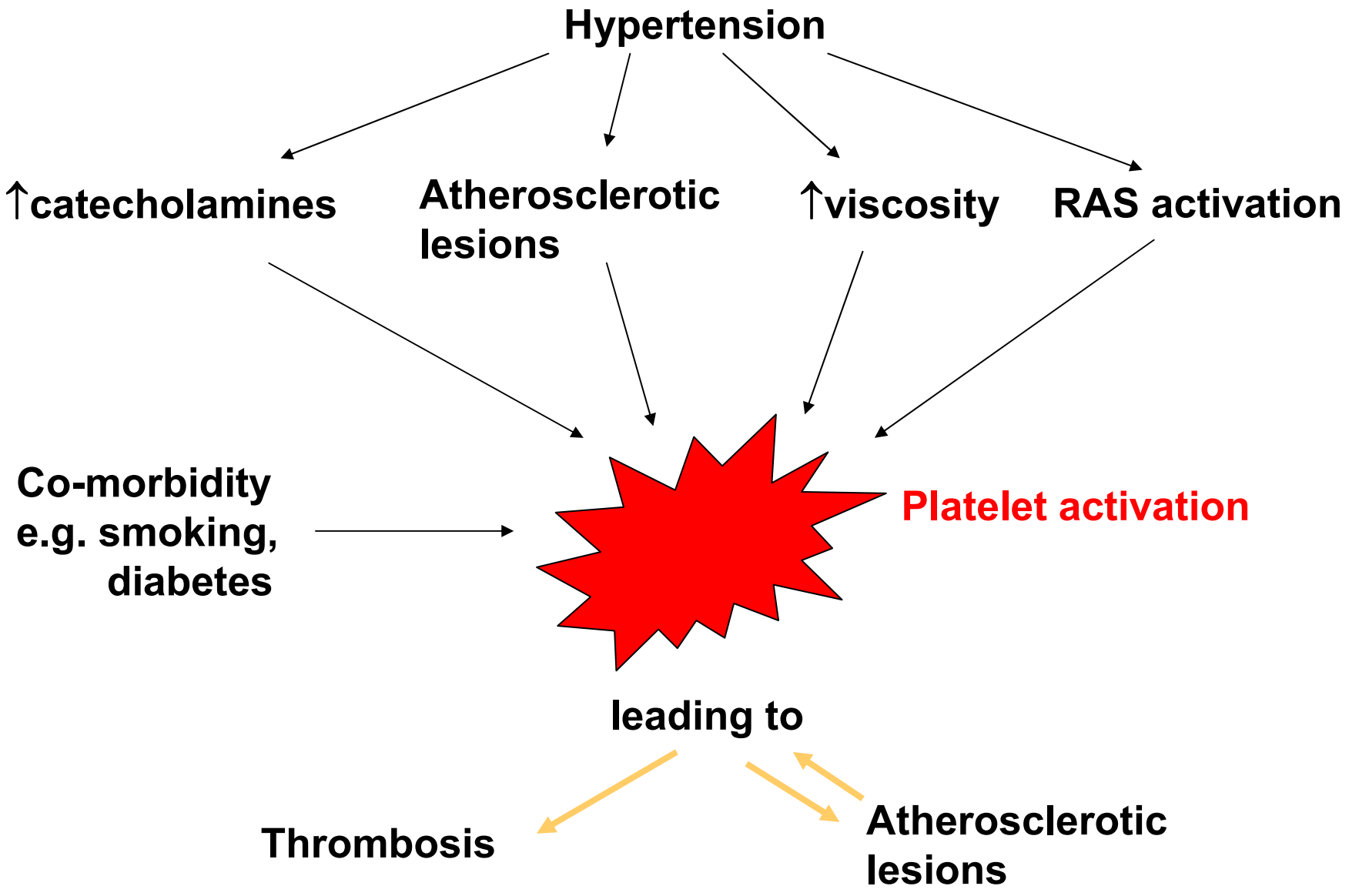
Dahlöf et al. *Lancet* 2002;359:995–1003

Reduction in Risk of Stroke in Patients with AF



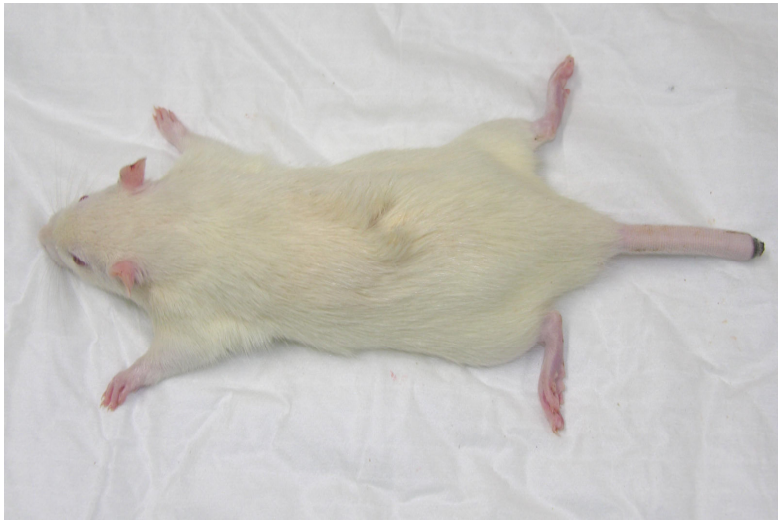
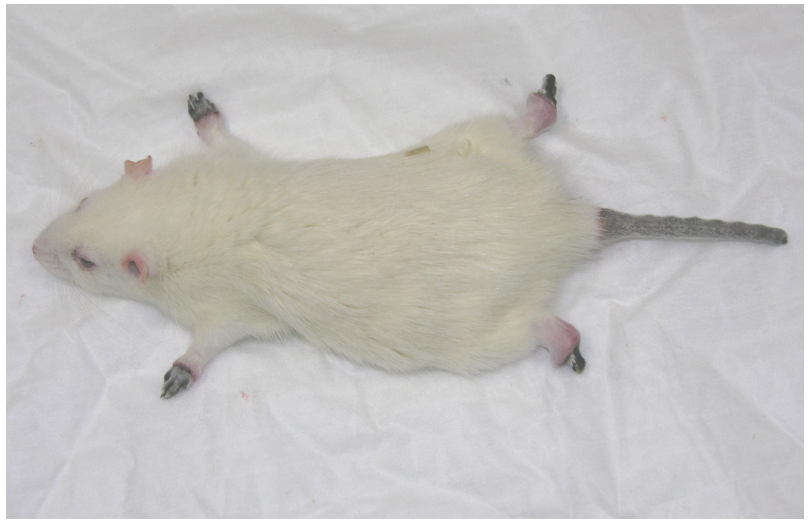
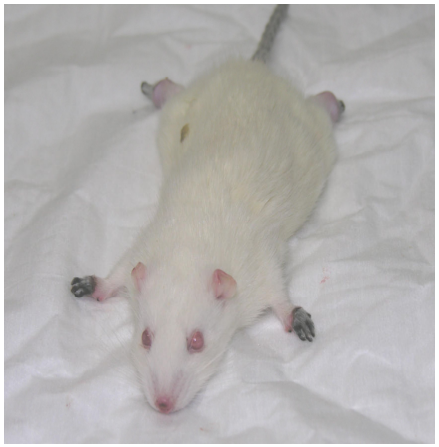
Dalhöf B et al. Presented at the European Society of Cardiology Congress; Berlin, Germany; August 31–September 4, 2002. Poster 2163.

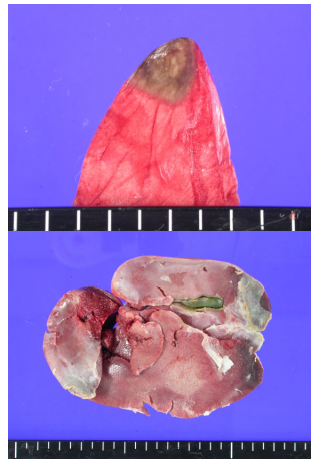
Platelet activation in hypertension



Blann, A. D. et al. Hypertension 2003;42:1-7

Induction of Inflammation & Arterial Thrombosis

KUMC Guro 2007

Changes Seen in Platelets With Hypertension

Morphological changes Increased volume Change in shape Increased turnover
Biochemical changes Increased intracellular free calcium Decreased calmodulin levels Increased sensitivity to catecholamines Higher density of adrenoceptors Decreased levels of intracellular catecholamines and serotonin
Functional changes Increased aggregability to agonists such as collagen and ADP Increased adhesiveness to molecules such as vitronectin and fibrin Increased spontaneous aggregation Increased expression of membrane markers, such as P-selectin Increased release of soluble markers from granules, such as beta thromboglobulin

Blann, A. D. et al. Hypertension 2003;42:1-7

ß-Blockers, α-Blockers, and Platelet Function

ß-Blockers			
Propranolol 80 mg BID	Hansen et al[61]	ADP-induced aggregation	Increased
Propranolol 40–120 mg	Ding et al[69]	ß thromboglobulin	Reduced
		Multiple aggregations	No effect
Propranolol 80 mg BID	Winther et al[52]	ADP-induced aggregation	Increased
Propranolol	Larsson et al[44]	Aggregability	No change
Bopindolol 1 mg BID	Winther et al[62]	ADP-induced aggregation	No change
Metoprolol 100 mg BID	Winther et al[63]	ADP-induced aggregation	No change
Atenolol 100 mg	Gleerup et al[70]	ß thromboglobulin	Reduced
	Smith et al[71]	ß thromboglobulin	Reduced
Atenolol 80 mg		Multiple aggregations	No change
Atenolol 50 mg	Knight et al[72]	Aggregation	Increased
α-Blockers			
Prazosin 2–8 mg	Okrucka et al[64]	ADP-induced aggregation	No change
Urapidil	Spah et al[65]	ADP-induced aggregation	Decrease
Terazosin 1–4 mg	Hernandez et al[66]	ADP-induced aggregation	No change
Doxazosin	Hernandez et al[67]	ADP-induced aggregation	Decreased
Doxazosin	Hernandez et al[68]	ADP-induced aggregation	Decreased
Phentolamine	Kimura and Okuda[59]	Epinephrine-induced calcium flux	Inhibition

ADP indicates adenosine diphosphate.

Blann, A. D. et al. Hypertension 2003;42:1-7

Calcium Channel Antagonists and Platelet Function

Nifedipine 20–40 mg BID	Birkebaek et al[79]	Platelet factor 4	No change
Isradipine 2.5 mg	Gleerup et al[15]	ADP-induced aggregation	Decreased
	Gleerup et al[70]	ß thromboglobulin	Decreased
		Platelet factor 4	Decreased
Diltiazem 60–180 mg	Pechan et al[100]	ADP-induced aggregation	Decreased
Nitrendipine 10–20 mg	Muller et al[82]	Platelet adrenoceptors	No change
Felodipine	Sengelov et al[102]	Platelet factor 4	Decreased
Amlodipine 10 mg	Hernandez-Hernandez et al[83]	ADP-induced aggregation	Decreased
Verapamil 80–200 mg	Ding et al[69]	ß thromboglobulin	Decreased
		Multiple aggregations	No effect
Verapamil	Addonizio et al[103]	ADP-induced aggregation	Decreased
Efonidipine 40 mg	Nomura et al[21]	Soluble P-selectin, $CD62^+$ platelets, microparticles	All decreased

Blann, A. D. et al. Hypertension 2003;42:1-7

ACE Inhibitors, Angiotensin II Antagonists, and Platelet Function

ACE inhibitors			
Captopril 25 mg BID	Someya et al[78]	ADP-induced aggregation	Decreased
Captopril 25–50 mg BID	Birkebaek et al[79]	ADP-induced aggregation, PF4	No change
Quinalapril 20 mg BID	Gupta et al[80]	ADP-induced aggregation, PF4	No change
Enalapril 10–20 mg	Li-Saw-Hee et al[81]	ADP-induced aggregation, PF4	No change
Captopril 25–50 mg	Muller et al[82]	Platelet -adrenoceptors	Decreased
Enalapril 20 mg	Hernandez-Hernandez et al[83]	ADP-induced aggregation	Increased
Angiotensin II antagonists			
Losartan 50–100 mg	Li-Saw-Hee et al[81]	Soluble P-selectin	No change
Losartan 50–100 mg	Pathansali et al[91]	Megakaryocyte size and ploidy	Decreased
		Bleeding time	Increased
		Aggregation	No effect
Losartan 100 mg	Levy et al[84]	Platelet aggregation	Decreased
Losartan and valsartan	Kalinowski et al[77]	NO release in vitro	Increased
		Collagen-induced aggregation	Decreased

PF4 indicates platelet factor 4; NO, nitric oxide.

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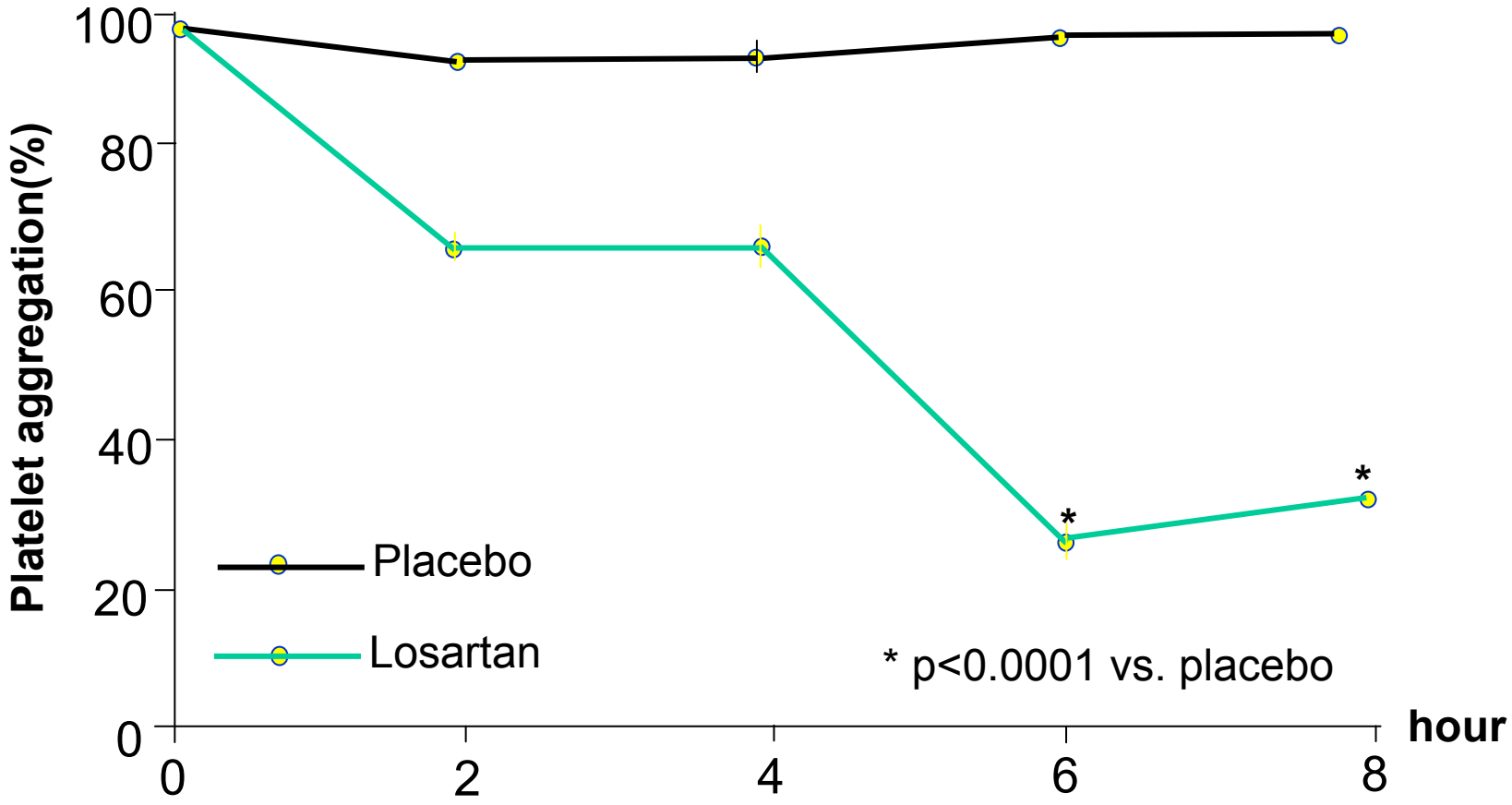
Losartan-dependent Inhibition of Platelet Aggregation *in vivo*



Kremer C et al Circ Res 2002;90:770-76

Effect of in vivo treatment of SHRSP with AT-1 antagonists on ex vivo platelet adhesion

Platelets	Platelet adhesion (%)
WKY	4.1 ± 2.3
SHRSP	22.7 ± 4.8[a]
SHRSP + losartan	8.1 ± 2.1[a,b]
SHRSP + valsartan	18.3 ± 4.0[a]
SHRSP + candesartan	21.0 ± 4.3[a]

Platelets were obtained from normotensive Wistar–Kyoto rats (WKY), stroke-prone spontaneously hypertensive rats (SHRSP), losartan-treated SHRSP (SHRSP + LOS) rats, valsartan-treated SHRSP (SHRSP + VAL) rats, and candesartan-treated SHRSP (SHRSP + CAN) rats. Platelets (5×10^8 platelets/well) were then incubated at 37°C for 1 h on a synthetic surface. Results are represented as means ± SEM.

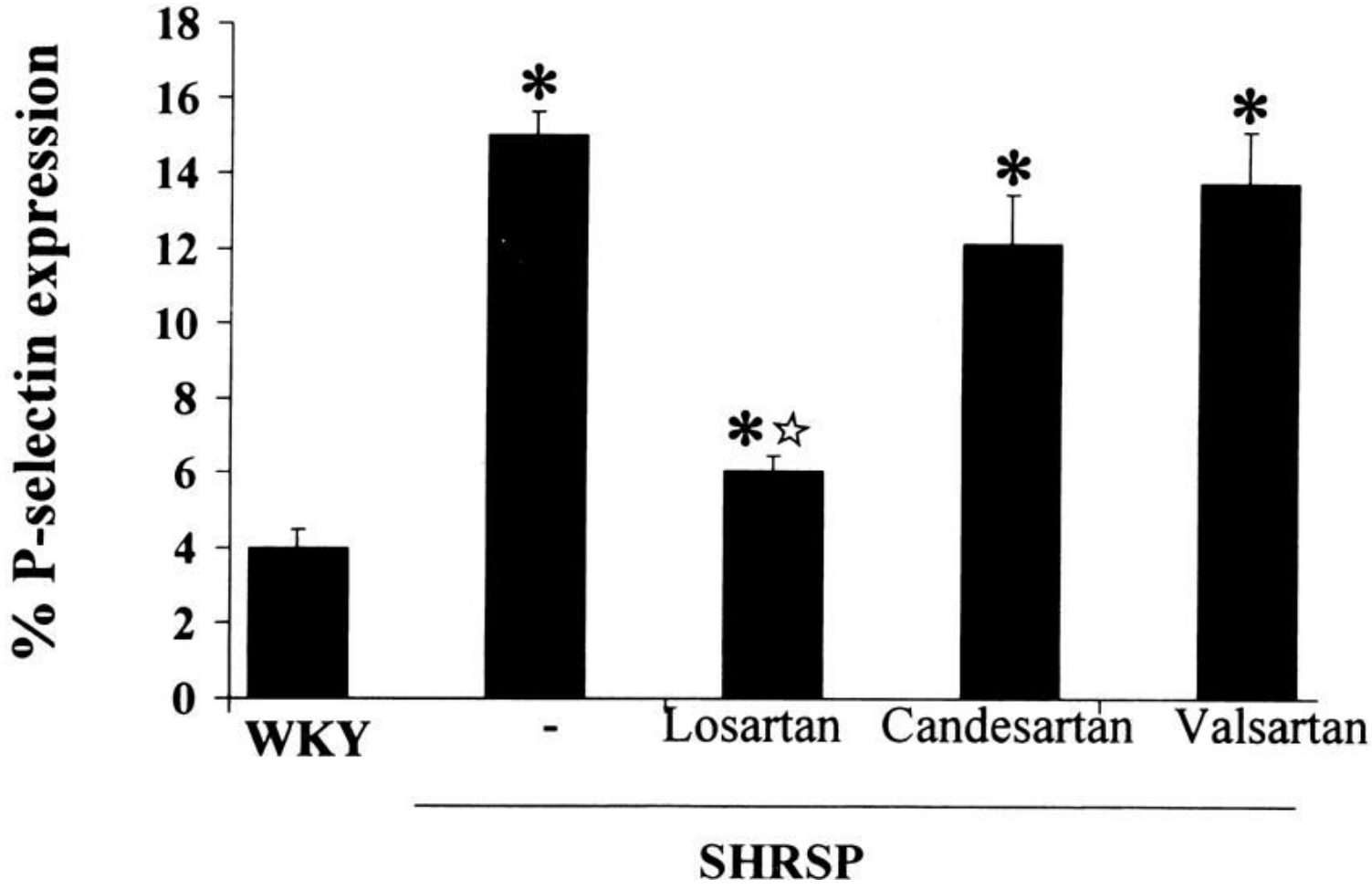
[a] $p < 0.05$ with respect to WKY.

[b] $p < 0.05$ with respect to untreated SHRSP.

AT-1, angiotensin II type 1.

Jimenez: J Cardiovasc Pharmacol, Volume 37(4).April 2001.406-412

% of P-selectin expression in platelets obtained from Wistar–Kyoto rats, stroke-prone spontaneously hypertensive rats, and SHRSP treated with losartan, candesartan, and valsartan for 14 days.

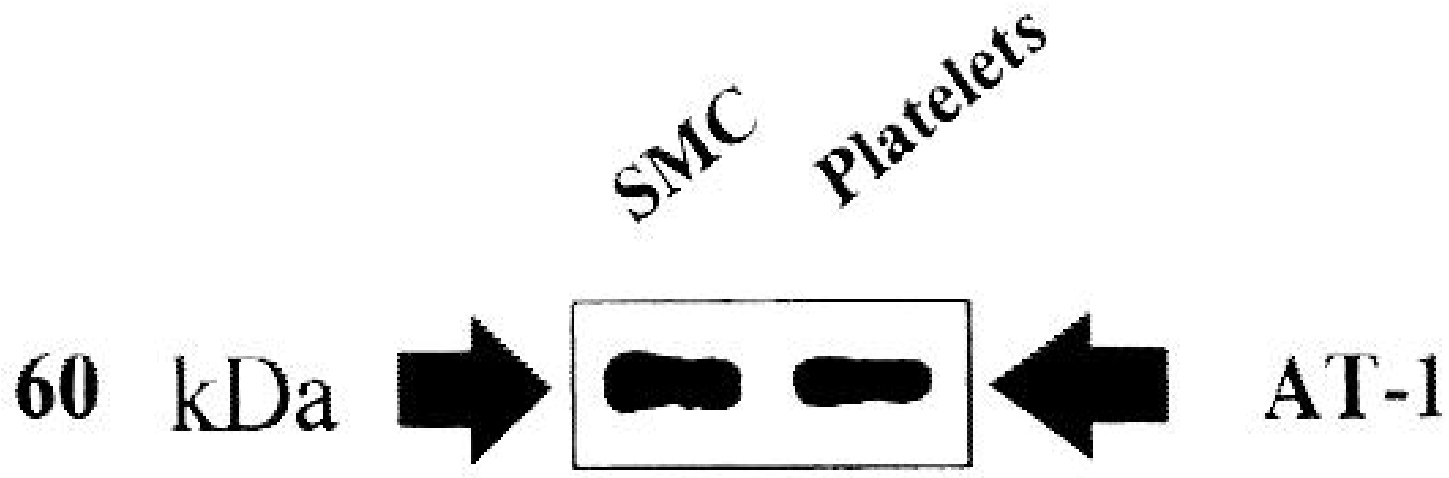


right shadowed white star]$p < 0.05$ with respect to SHRSP.

Jimenez: J Cardiovasc Pharmacol, Volume 37(4).April 2001.406-412

AT-1-induced Effect on Platelets

Western blot demonstrating the presence of AT-1-type receptors in human platelets.



Monton: J Cardiovasc Pharmacol, Volume 35(6).June 2000.906-913

Effect of ANG II and the blockade of AT-1 and AT-2 receptors on the antiplatelet effect of irbesartan and losartan

	Light transmission (%)
—	72 ± 4[a]
Losartan	45 ± 3
Irbesartan	42 ± 3
PD123319	75 ± 3[a]
Losartan + PD123319	44 ± 3
Irbesartan + PD123319	41 ± 4
Ang II	74 ± 2[a]
Ang II + losartan	44 ± 2
Ang II + irbesartan	41 ± 2
EXP3174 + losartan	43 ± 3
EXP3174 + irbesartan	40 ± 4

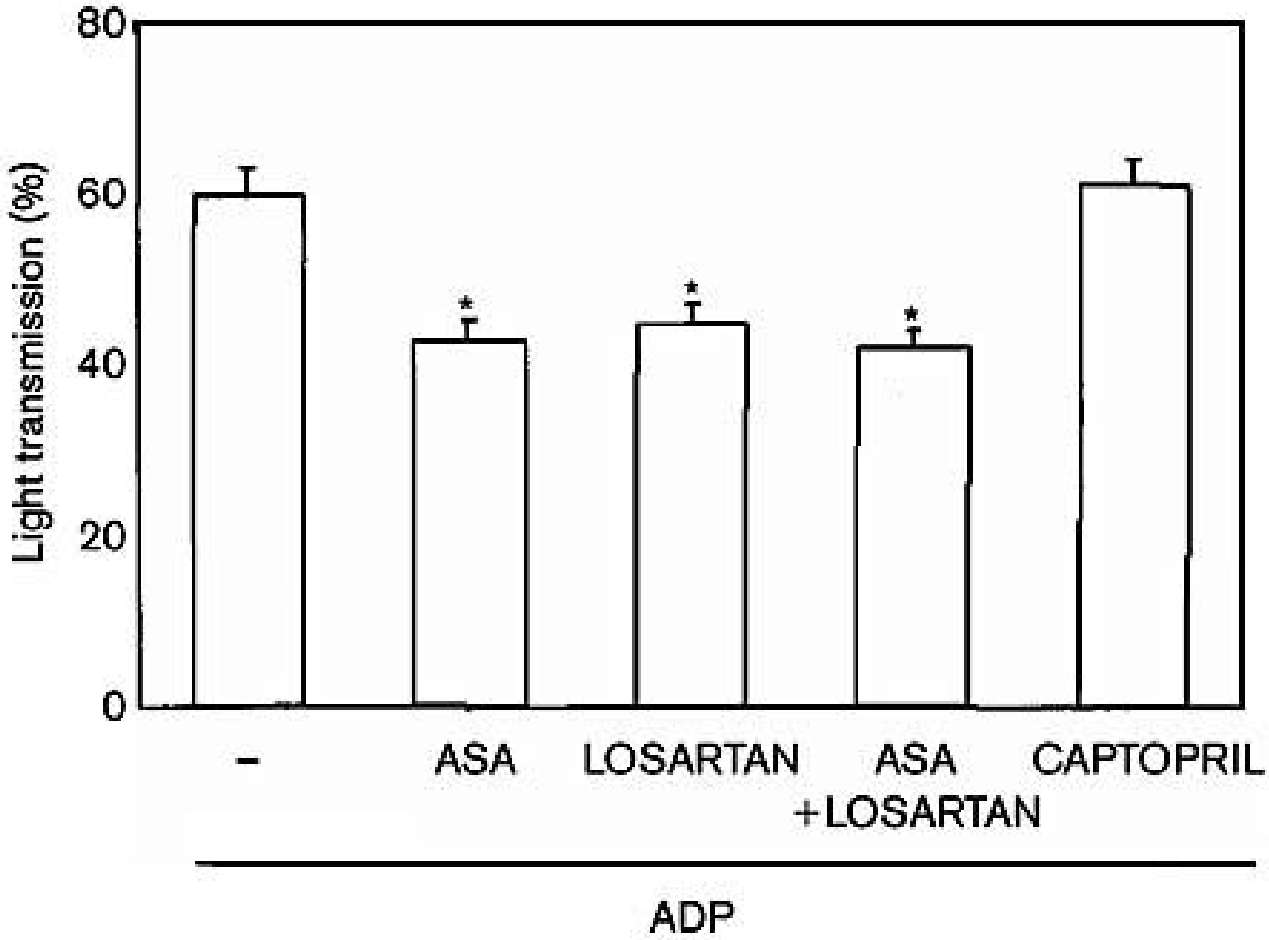
Platelets were activated with 10^{-6} M U446619 in the presence and in the absence of losartan (5×10^{-5} M), irbesartan (5×10^{-5} M), PD123319 (10^{-8} M), angiotensin II (Ang II, 10^{-7} M) and EXP3174 (5×10^{-5} M). Data are represented as mean ± SEM of six different experiments.

[a] $p < 0.05$ with respect to losartan and irbesartan alone.

Monton: J Cardiovasc Pharmacol, Volume 35(6).June 2000.906-913

ADP-induced Effect on Platelets

ADP-induced human platelet activation in the presence or absence of aspirin, losartan and captopril.



Spontaneous platelet activation (< 5%) was not changed by any of the three substances. Data are means ± SEM of 15 experiments.

*$P < 0.05$, versus ADP alone.

Guerra Cuesta: J Hypertens, Volume 17(3).March 1999.447–452

Effect of AT-1-receptor antagonist on ADP-induced platelet activation

	Light transmission (%)	
	−ASA	+ASA
—	62 ± 3	40 ± 3[a]
Losartan	39 ± 2[a]	38 ± 3[a]
Irbesartan	38 ± 4[a]	37 ± 5[a]
Telmisartan	48 ± 3[ab]	40 ± 4[a]
EXP3174	54 ± 1[ab]	42 ± 3[a]
Valsartan	53 ± 3[ab]	42 ± 5[a]
CV11974	60 ± 5[b]	39 ± 3[a]

Platelets were activated with 10^{-5} M ADP in the presence and in the absence of aspirin (ASA, 3×10^{-3} M), losartan (5×10^{-5} M), irbesartan (5×10^{-5} M), telmisartan (5×10^{-5} M), EXP3174 (5×10^{-5} M), valsartan (5×10^{-5} M), and CV11974 (5×10^{-5} M). Data expressed as mean ± SEM of six different experiments.

[a] $p < 0.05$ with respect to ADP alone.

[b] $p < 0.05$ with respect to losartan and irbesartan.

Monton: J Cardiovasc Pharmacol, Volume 35(6).June 2000.906-913

TxB2 released by ADP-stimulated platelets

	TxB_2 (ng)
—	4.2 ± 0.3
Aspirin	0.5 ± 0.02^a
Losartan	4.0 ± 0.2
Irbesartan	4.2 ± 0.2
Telmisartan	4.1 ± 0.2
EXP3174	4.0 ± 0.1
Valsartan	3.9 ± 0.2
CV11974	3.9 ± 0.3

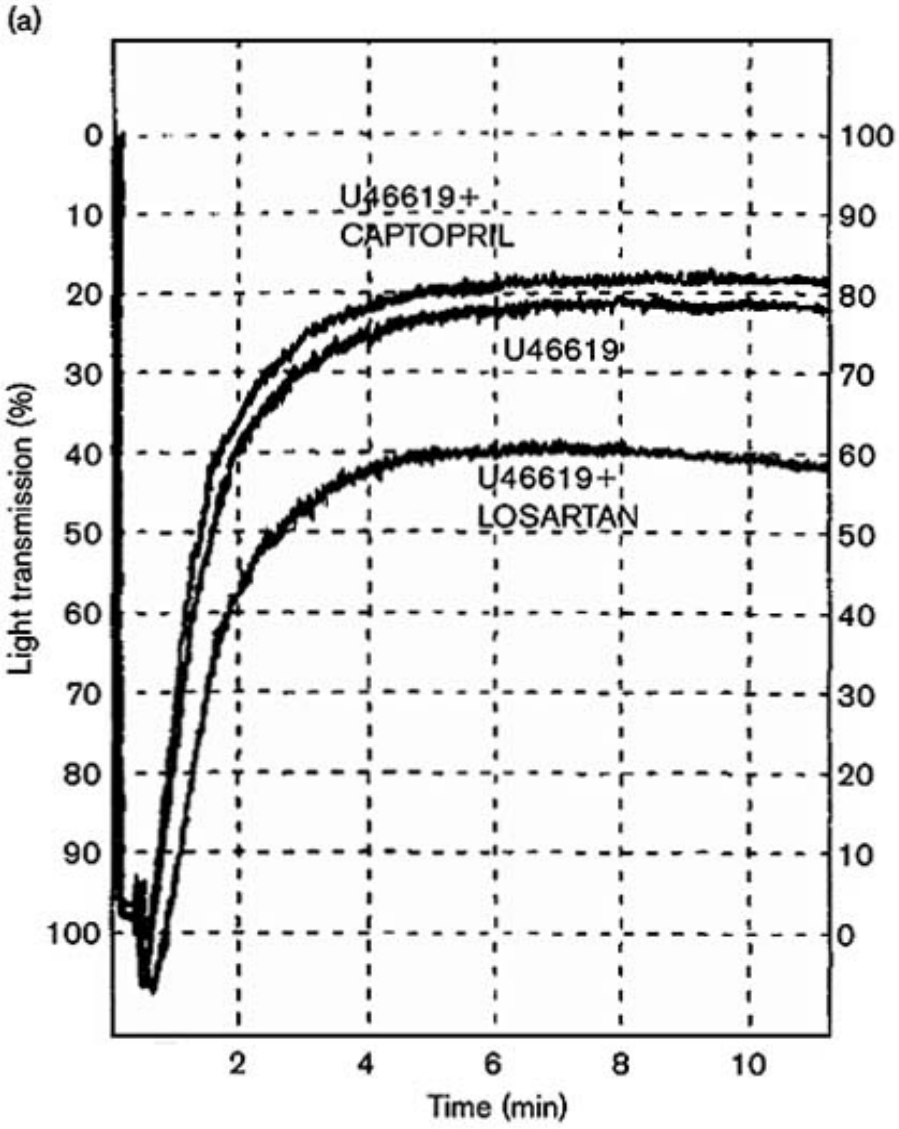
Platelets were activated with 10^{-5} M ADP in the presence and in the absence of aspirin (3×10^{-3} M) and the different AT-1–receptor antagonists. The concentration used for each AT-1 antagonist was 5×10^{-5} M. Data represent the mean ± SEM of six different experiments.

$^a p < 0.05$ with respect to ADP-stimulated platelets.

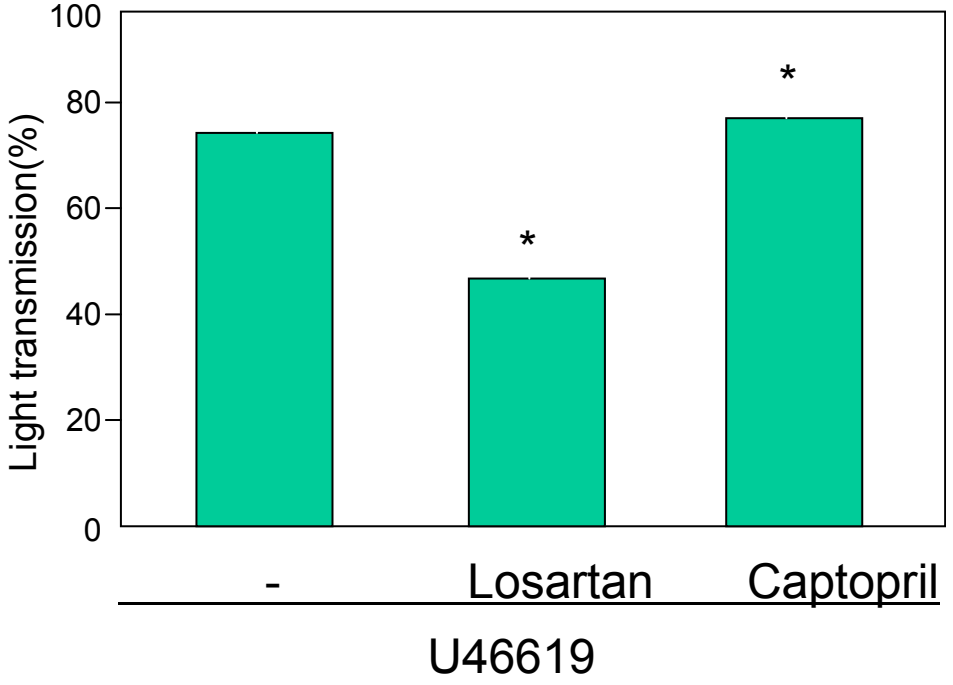
Monton: J Cardiovasc Pharmacol, Volume 35(6).June 2000.906-913

TXA2 inhibition Effect on Platelets

U46619 -induced platelet activation in the presence of captopril or losartan.



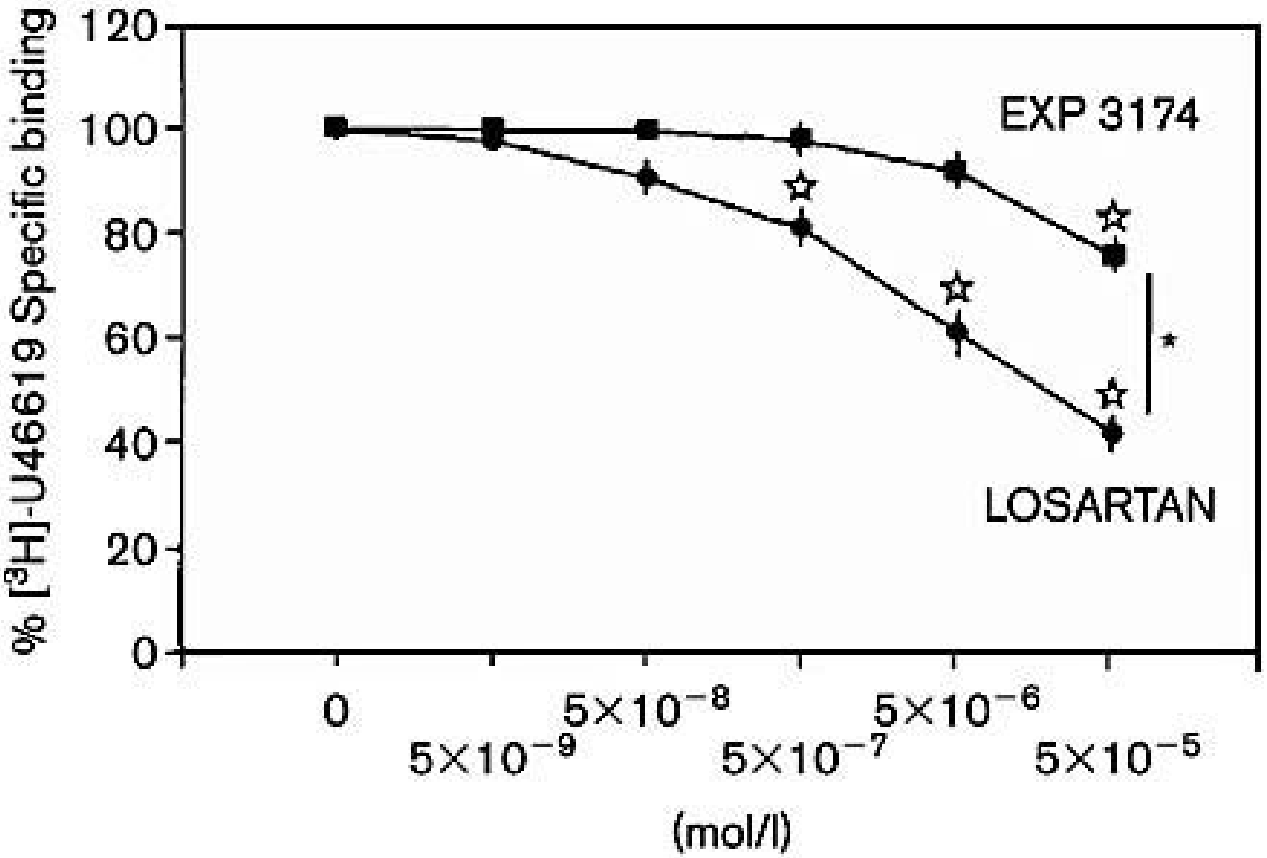
Inhibition of platelet activation by losartan or captopril 6 min after the addition of U46619



*$P < 0.05$, versus U46619 alone.

Guerra Cuesta: J Hypertens 1999.447–452

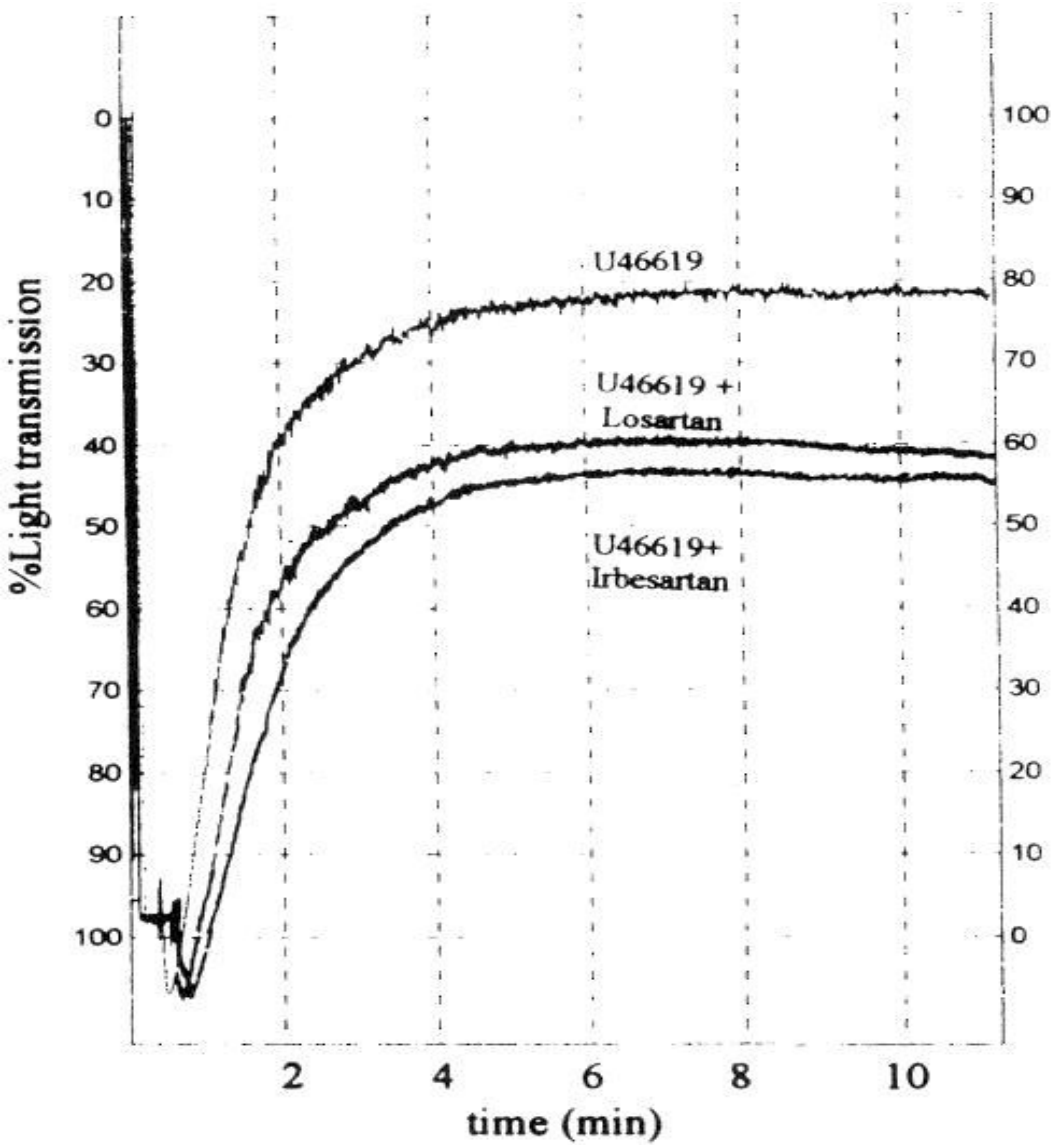
Displacement of [3H]-U46619 by unlabelled losartan and EXP 3174.



The platelet suspension was incubated with 4 nmol/l[3H]-U46619 in the presence or absence of increased concentrations of losartan and EXP 3174.
Specific binding was calculated using incubations with a 1000-fold excess of unlabeled U46619. Data are means ± SEM of five experiments.
*$P < 0.05$, versus EXP 3174; [white star]$P < 0.05$, versus no corresponding drug.

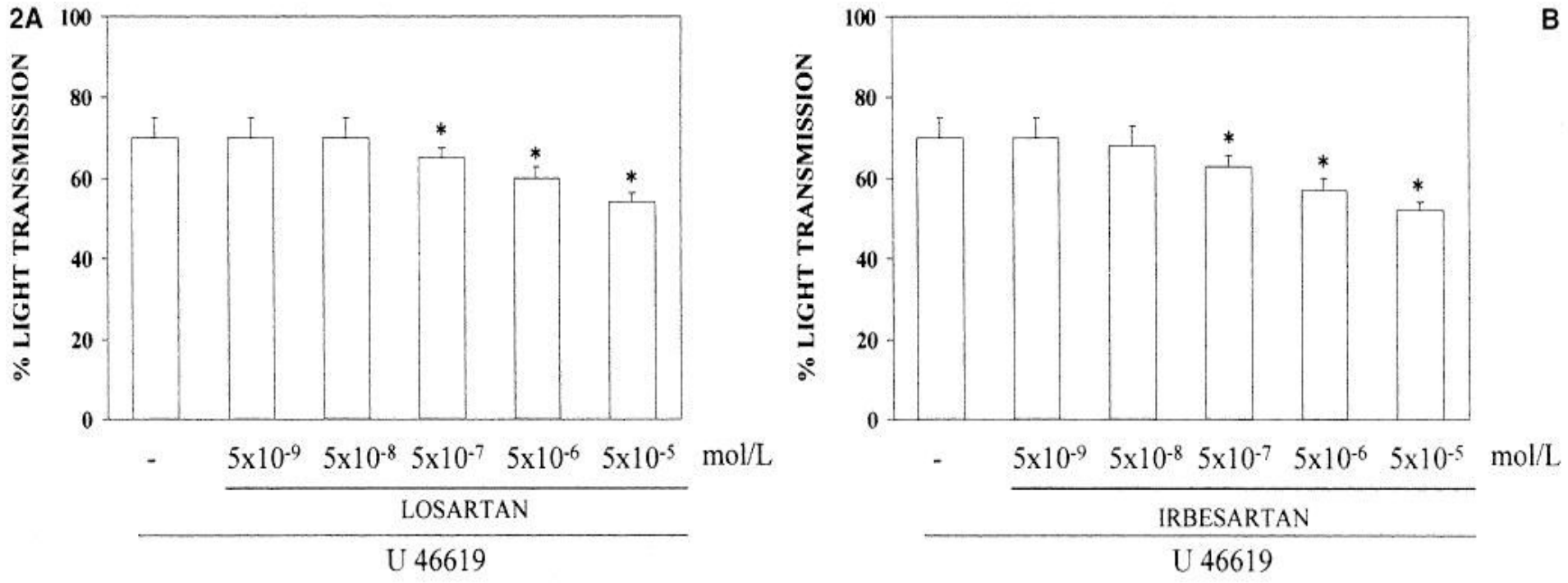
Guerra Cuesta: J Hypertens, Volume 17(3).March 1999.447–452

Representative trace showing U46619-induced platelet activation in the presence and in the absence of losartan and irbesartan .



Monton: J Cardiovasc Pharmacol, Volume 35(6).June 2000.906-913

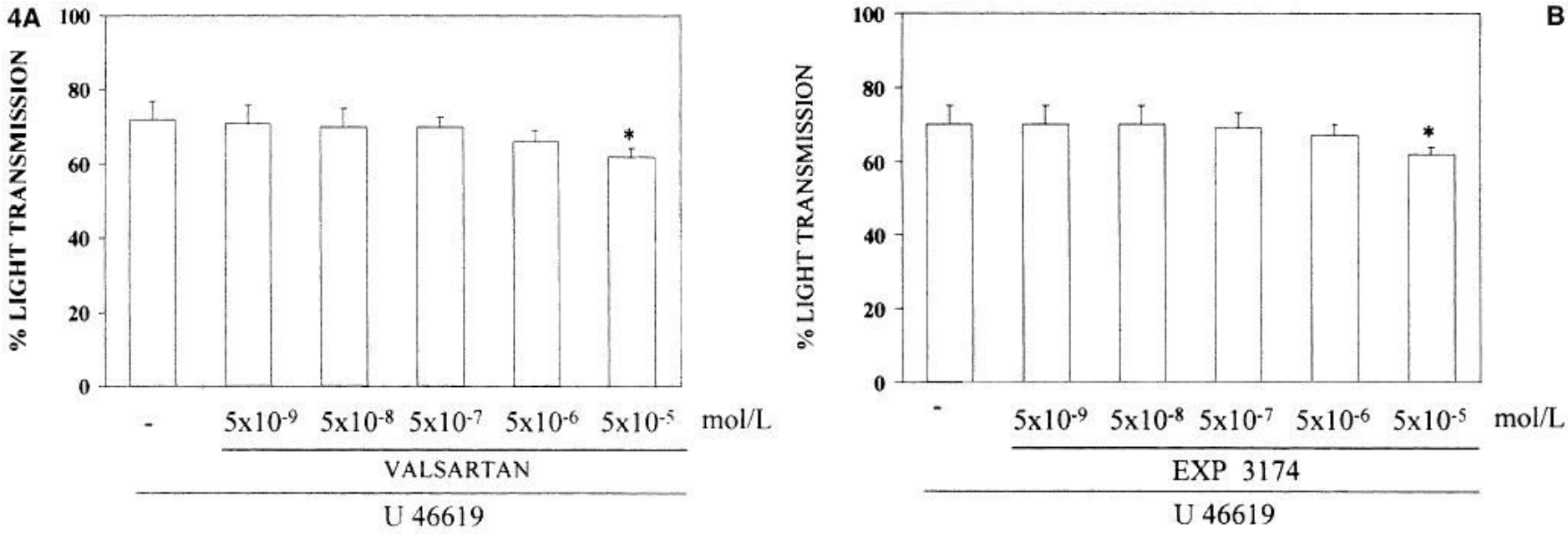
Effect of increasing concentrations of losartan **(A)** and irbesartan **(B)** on thromboxane A2 analogue U46619-induced platelet activation.



Platelet activation is plotted as percentage of light transmission 6 min after the addition of U46619. Data are expressed as mean ± SEM of six different experiments. *$p < 0.05$ with respect to U46619 alone.

Monton: J Cardiovasc Pharmacol, Volume 35(6).June 2000.906-913

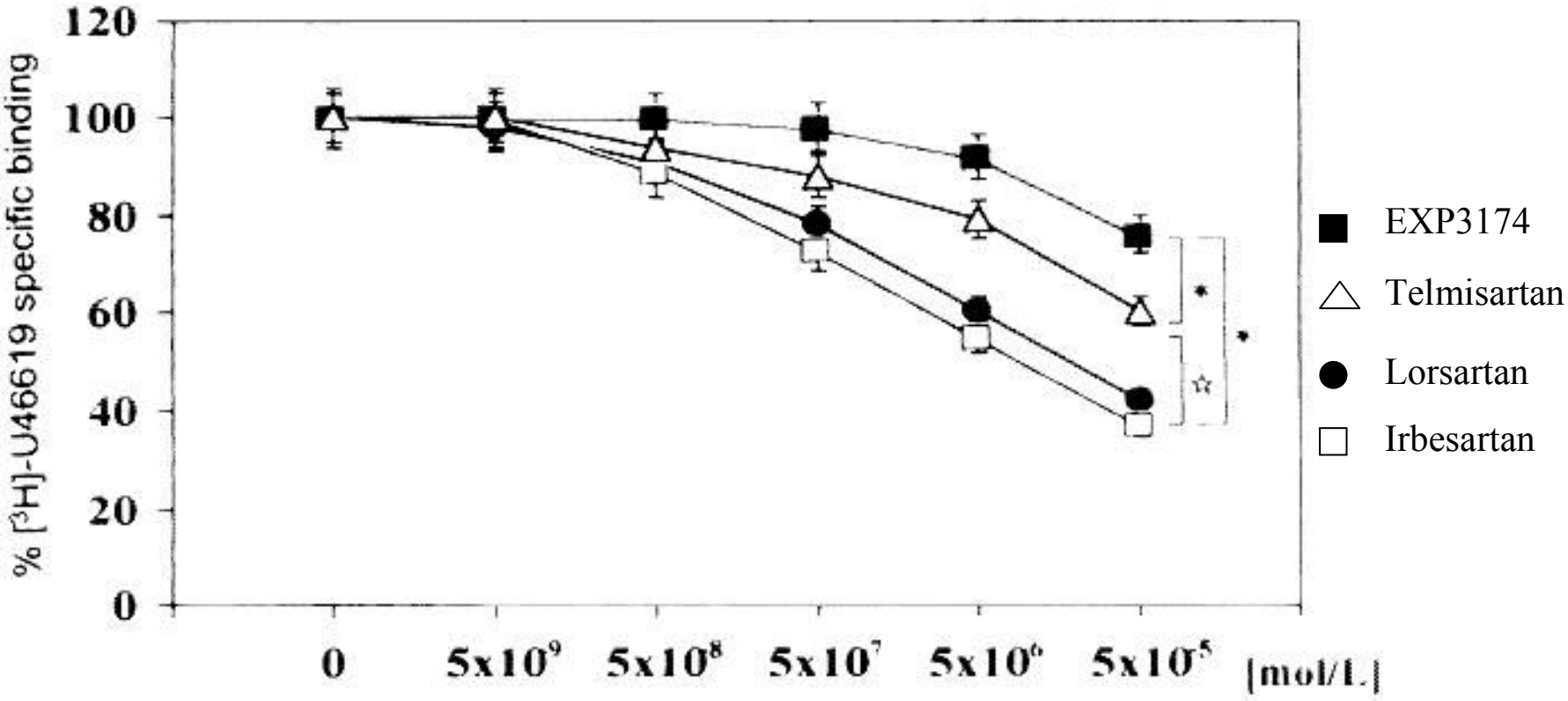
Effect of increasing concentrations of valsartan and the main hepatic Active metabolite of losartan, EXP3174, on thromboxane A2 analogue U46619-induced platelet activation.



Platelet activation is plotted as percentage of light transmission 6 min after the addition of U46619. Data are expressed as mean ± SEM of six different experiments. *$p < 0.05$ with respect to U46619 alone.

Monton: J Cardiovasc Pharmacol, Volume 35(6).June 2000.906-913

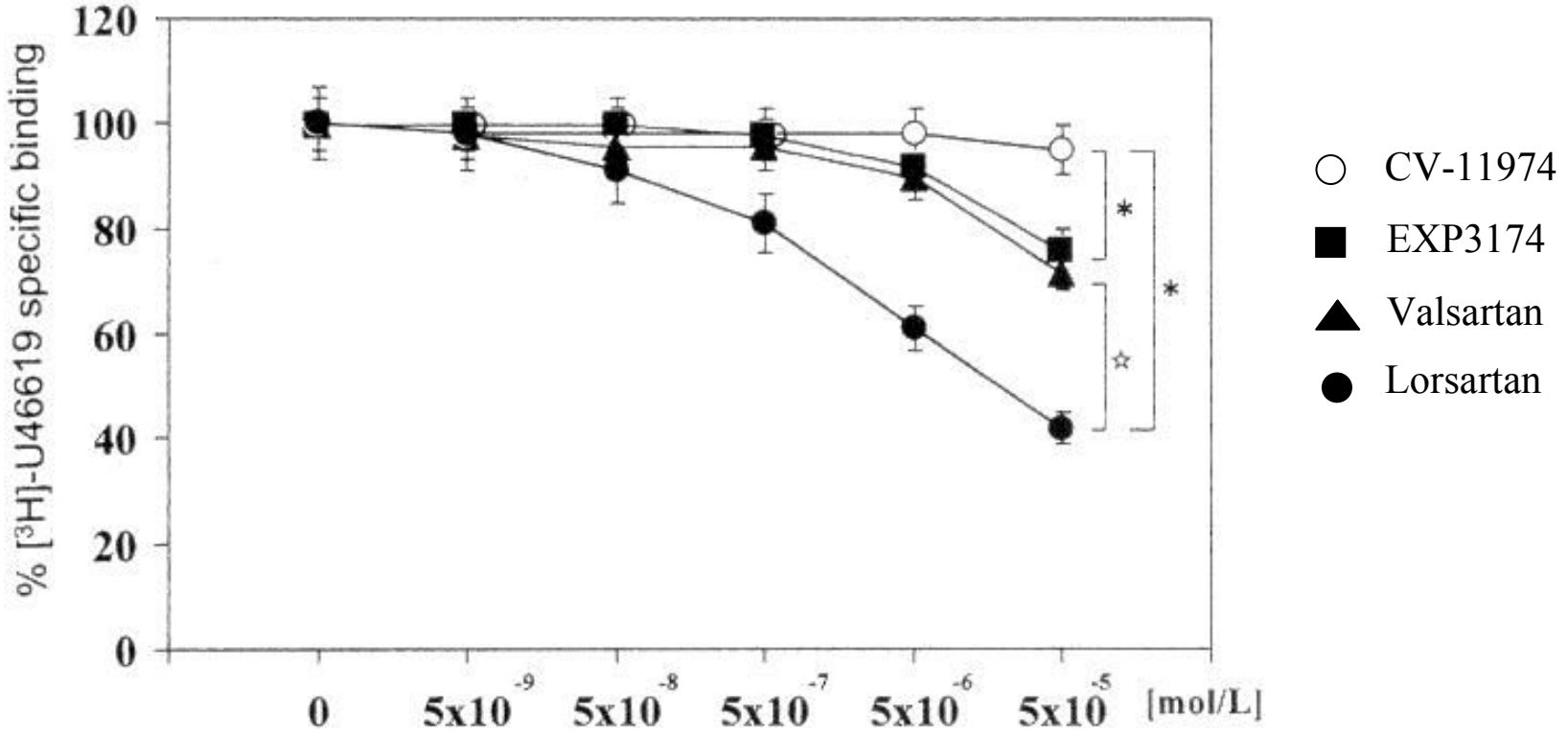
Displacement of [^{3}H]-U46619 from platelets by unlabeled losartan, irbesartan, EXP3174, and telmisartan.



Data are expressed as mean ± SEM of six different experiments.
*p < 0.05 with respect to EXP3174. [white star]p < 0.05 with respect to losartan and irbesartan.

Monton: J Cardiovasc Pharmacol, Volume 35(6).June 2000.906-913

Displacement of [^{3}H]-U46619 from platelets by unlabeled losartan, EXP3174, valsartan, and CV-11974.



The platelet suspension was incubated with 4 n*M* [3H]-U46619 in the presence and in the absence of increasing concentrations of each AT-1 antagonist.
*p < 0.05 with respect to CV-11974 antagonists. [white star]p < 0.05 with respect to EXP3174

Monton: J Cardiovasc Pharmacol, Volume 35(6).June 2000.906-913

Effect of in vitro addition of different AT-1 antagonists on U46619-induced in vitro platelet activation

Platelets	Platelet adhesion (%)
Basal	4.0 ± 2.2
U46619	25.9 ± 1.9[a]
U46619 + losartan	13.7 ± 3.3[a,b]
U46619 + valsartan	23.4 ± 2.1[a]
U46619 + candesartan	24.8 ± 3.1[a]

Platelets (5×10^8 platelets/well) from normotensive Wistar–Kyoto rats were isolated and incubated in the absence (basal) and in the presence of the thromboxane analogue, U46619 (10^{-6} *M*) on a synthetic surface at 37°C for 1 h. Additional experiments were performed in the presence of losartan (5×10^{-6} *M*), valsartan (5×10^{-6} *M*), and candesartan (5×10^{-6} *M*). Results are represented as means ± SEM of six different experiments.

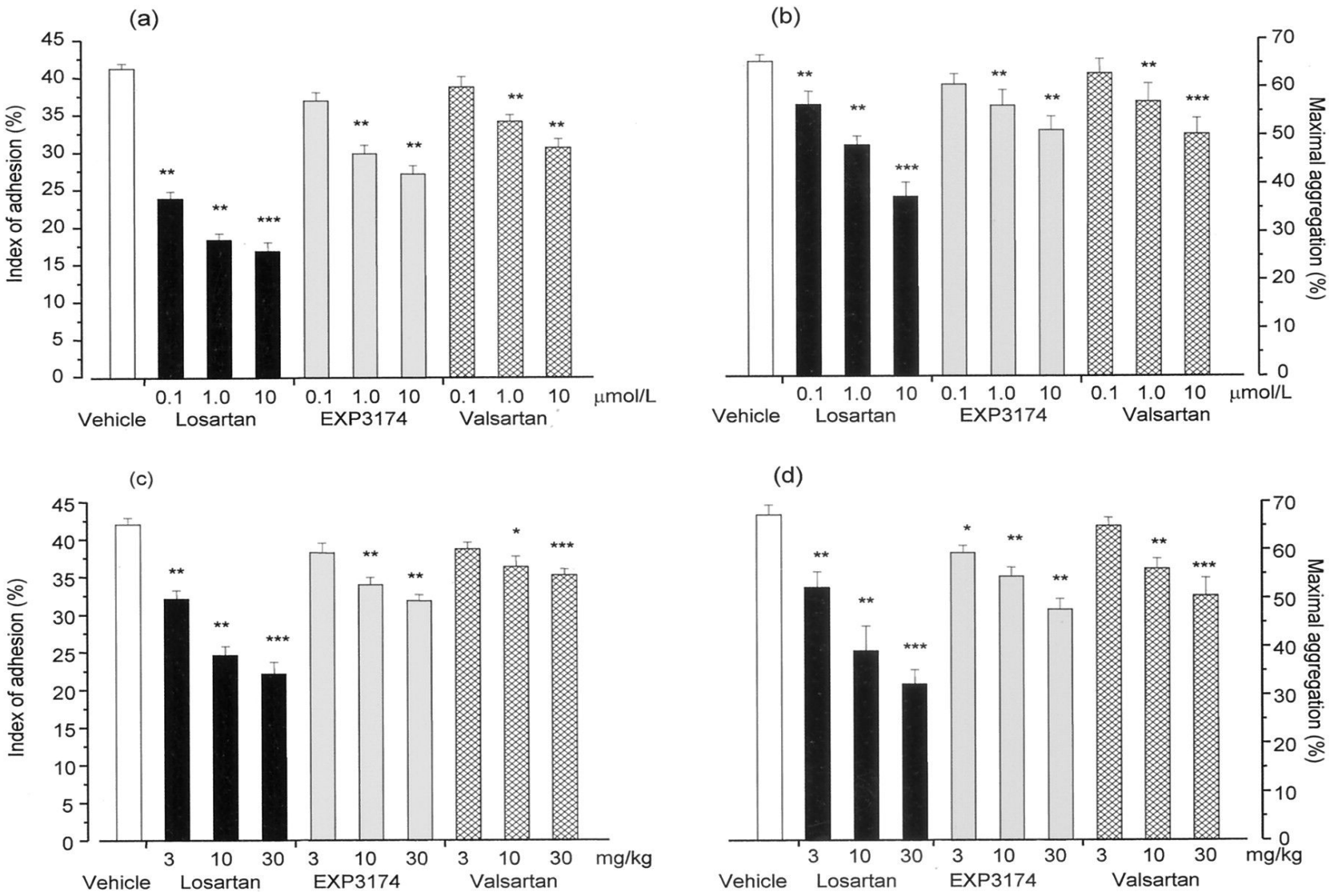
[a] $p < 0.05$ with respect to basal level.

[b] $p < 0.05$ with respect to U46619 in the absence of the angiotensin II type 1 (AT-1) antagonists.

Jimenez: J Cardiovasc Pharmacol, Volume 37(4).April 2001.406-412

Collagen-induced Effect on Platelets

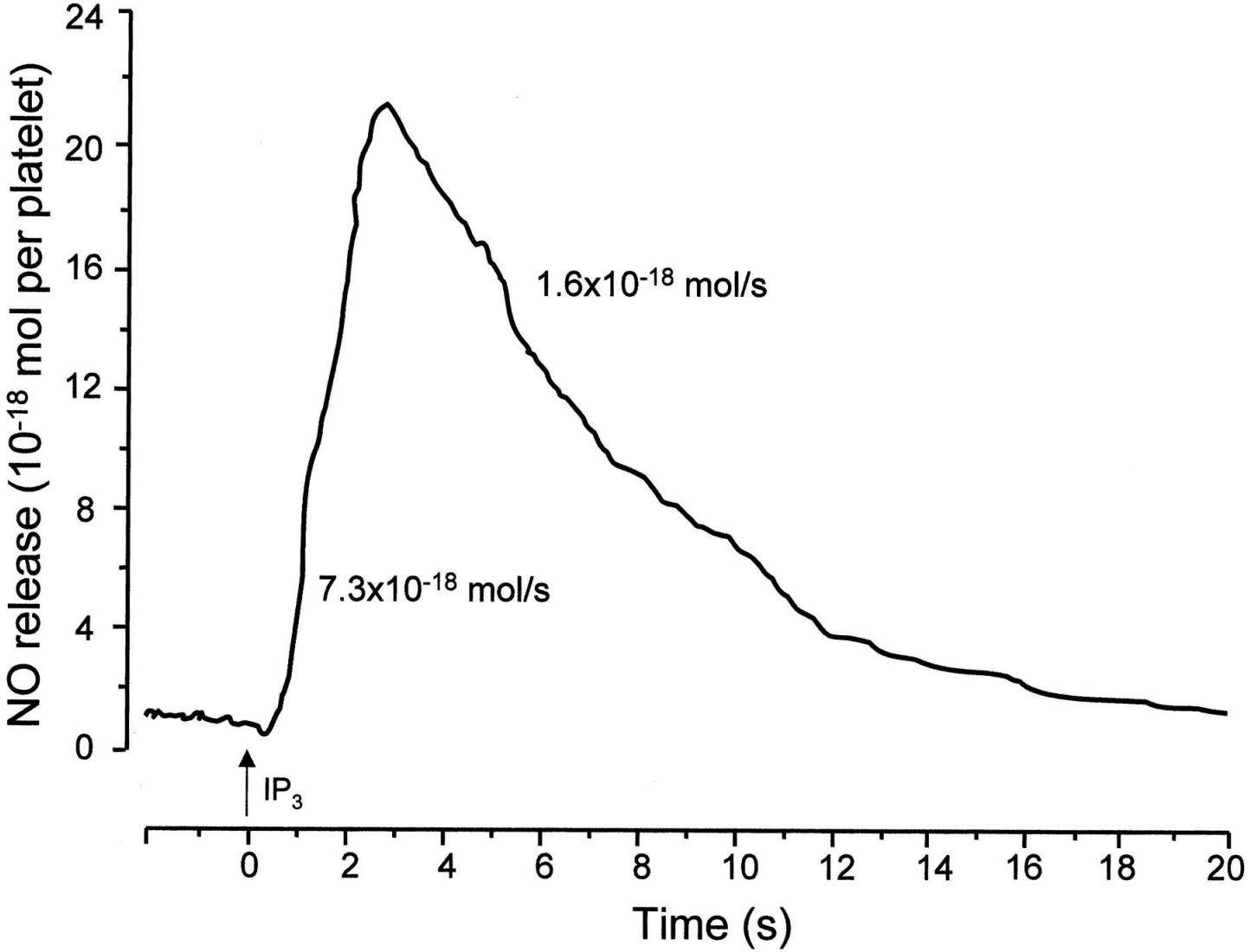
Dose-dependent effect of losartan, EXP3174, and valsartan on collagen-stimulated adhesion and U46619-stimulated aggregation of rat platelets in in vitro (a and b) and ex vivo (c and d) experiments



Kalinowski, L. et al. Hypertension 2002;40:521-527

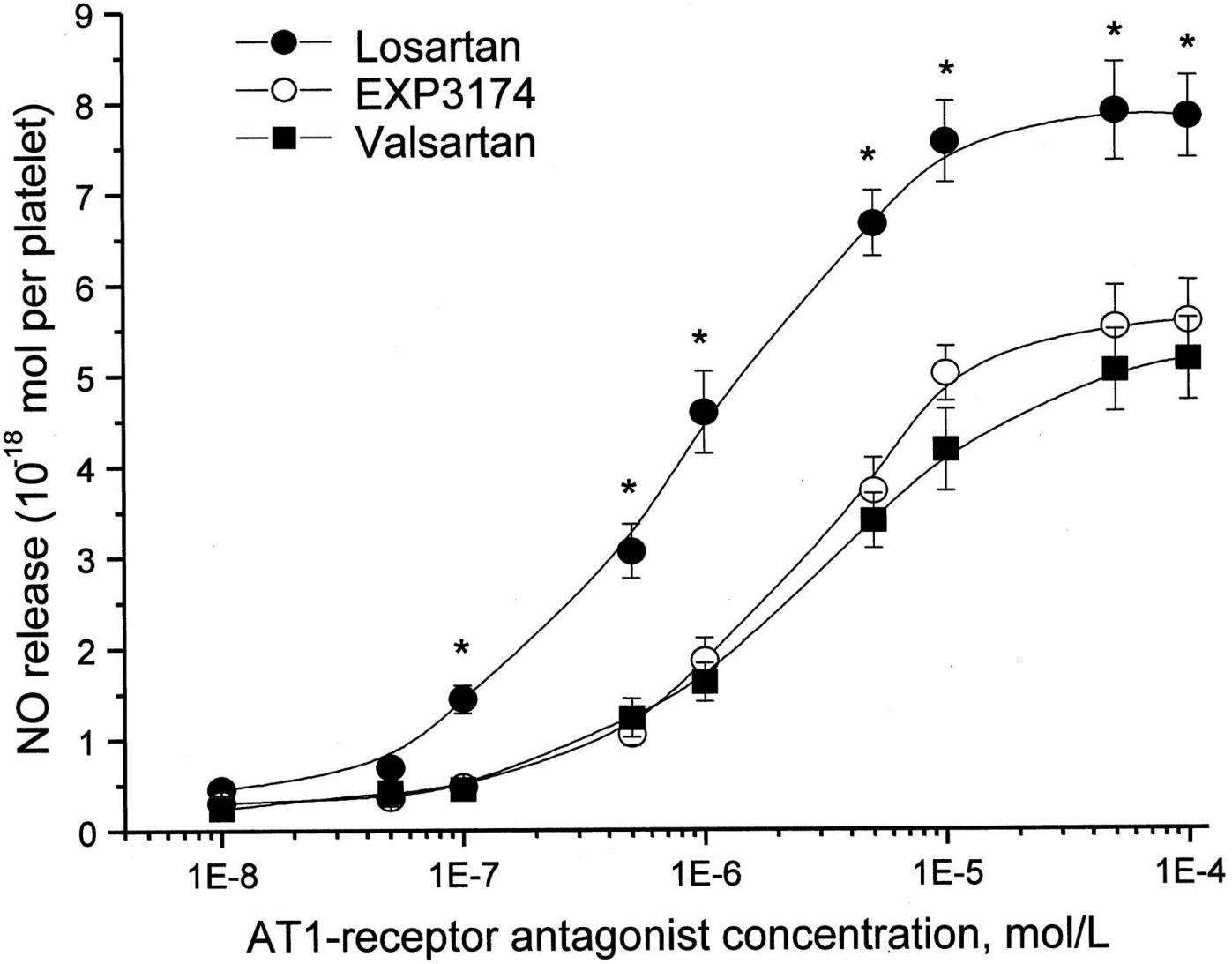
Mechanism of anti-platelet action of Losartan

NO release from platelets after stimulation with IP3



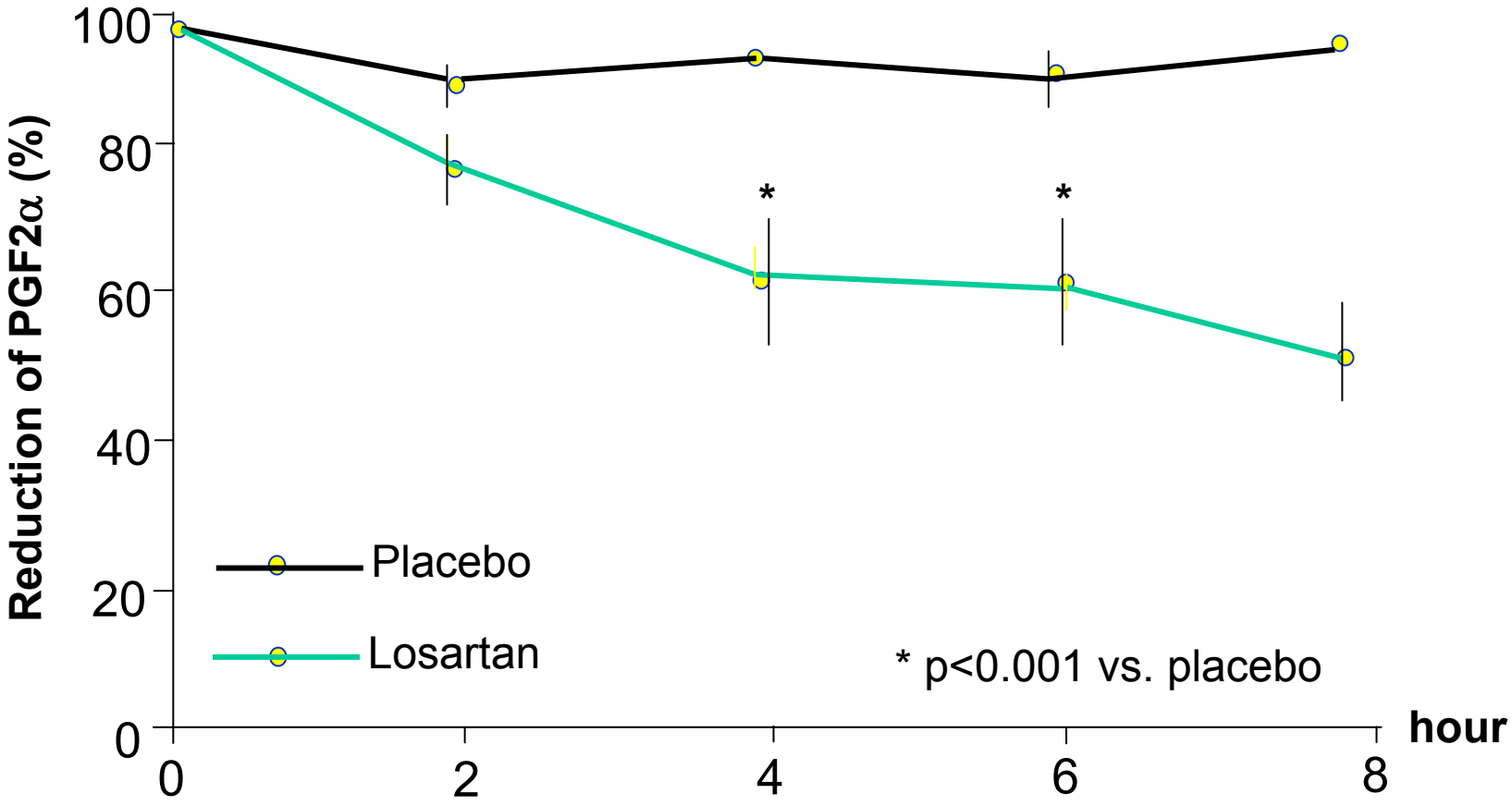
Kalinowski, L. et al. Hypertension 2002;40:521-527

NO release from platelets in dose-dependent response to the AT1 receptor antagonists: losartan, EXP3174, and valsartan (n=6)



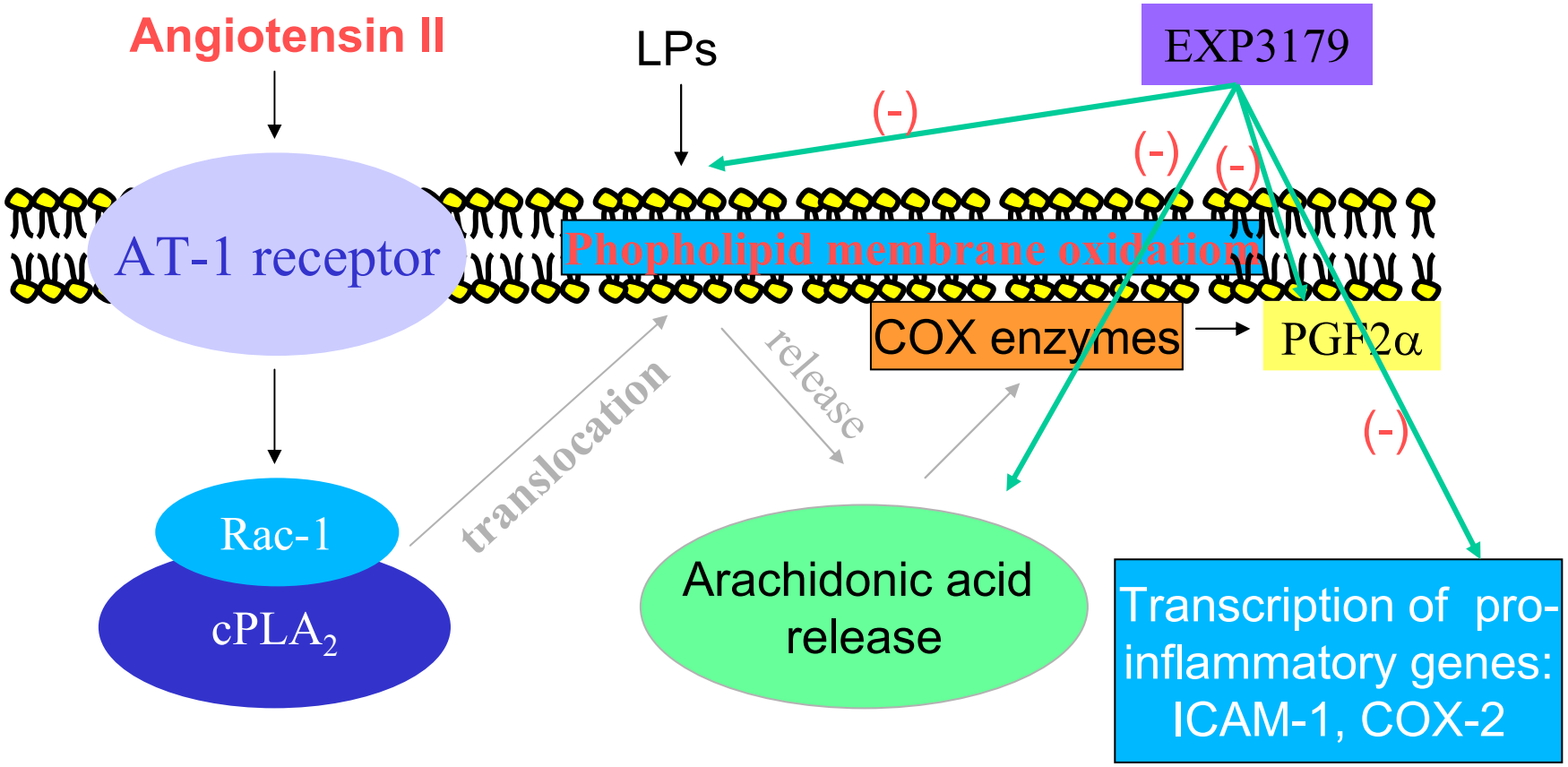
Kalinowski, L. et al. Hypertension 2002;40:521-527

Losartan-dependent Inhibition of PGF2α *in vivo*



Kremer C et al Circ Res 2002;90:770-76

Hypothetical Model of EXP3179 antiinflammatory and antiaggregatory properties



Krämer C et al. Circ Res. 2002;90:770-776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