ACE Inhibitors and Coronary Circulation

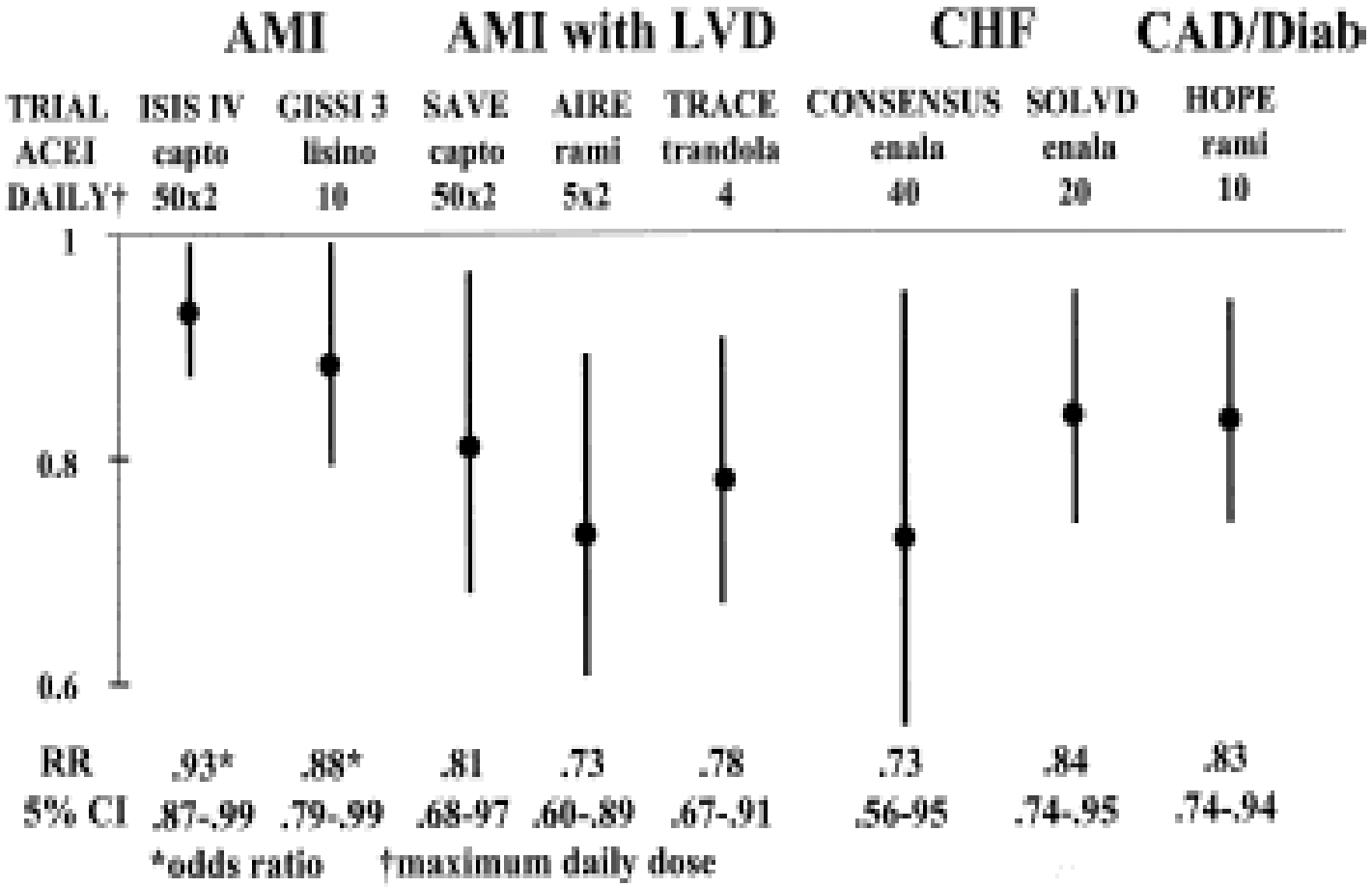
Georgios I. Papaioannou, MD

Hartford Hospital 6/4/2002

Objectives

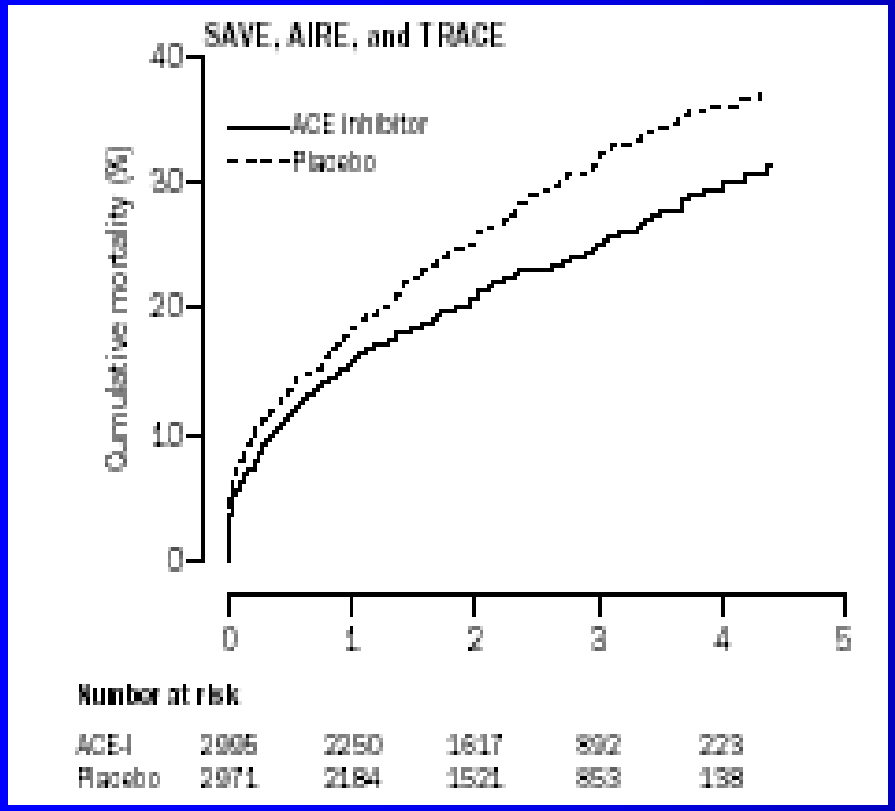
- **Impact of ACE-Inhibitors on atherosclerotic heart disease**
- ACE-Inhibitors and coronary microcirculation
- Anti-ischemic effect of ACE-Inhibitors in patients with risk factors for CAD or documented CAD
- Future directions - ACE genotyping

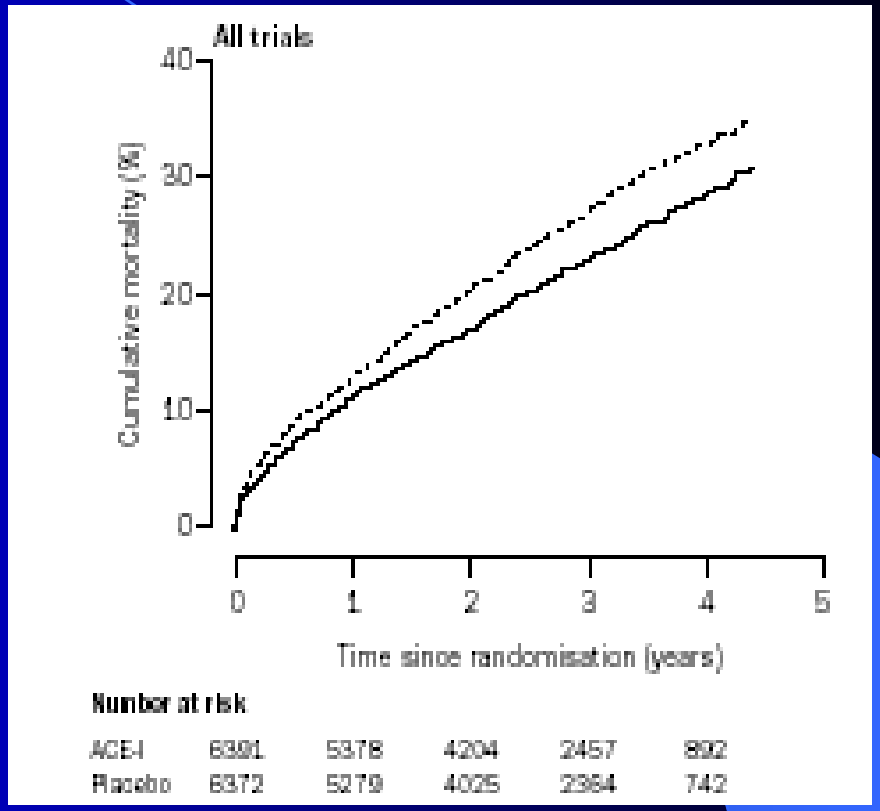
ACE-Inhibitors and CVS Disease



Mortality findings (RR ± 95% CI) in the large placebo-controlled ACE-Inhibitor trials of patients with AMI, AMI with LV dysfunction, CHF and CAD/DM. **J Am Coll Cardiol 2001;37:1456-60.**

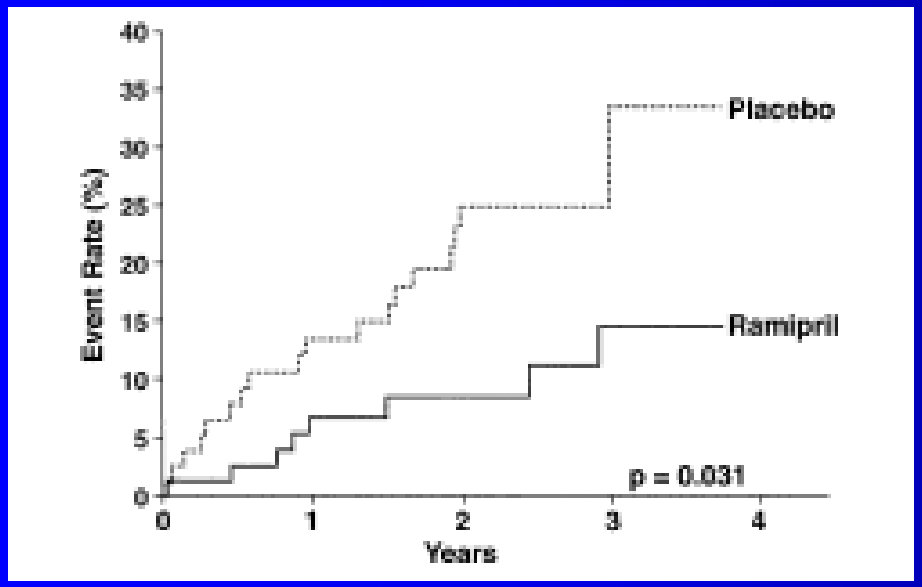
Long-term ACE-Inhibition in patients with CHF and/or LV dysfunction



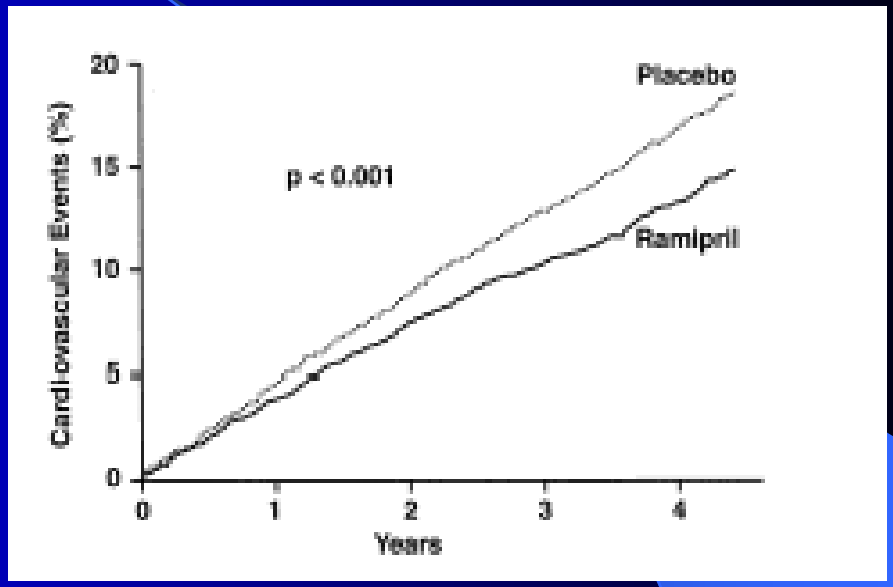


SAVE, AIRE, TRACE versus all Trials: **Mortality** over 4 years. **Lancet 2000;355:1575-81.**

Expanded indications for ACE-Inhibitors



Survival curves from the APRES study. The ramipril group experienced significantly fewer cardiovascular effects during the follow-up period. **J Am Coll Cardiol 2000;35:881-8.**



The occurrence of MI, stroke, or CVS death in the HOPE study. The ramipril group did substantially better than the placebo group (RR=0.78, 95% CI=0.70-0.86). **N Engl J Med 2000;342:145-53.**

ACE-Inhibitors in patients with DM

p=0.0004 **p=0.004**

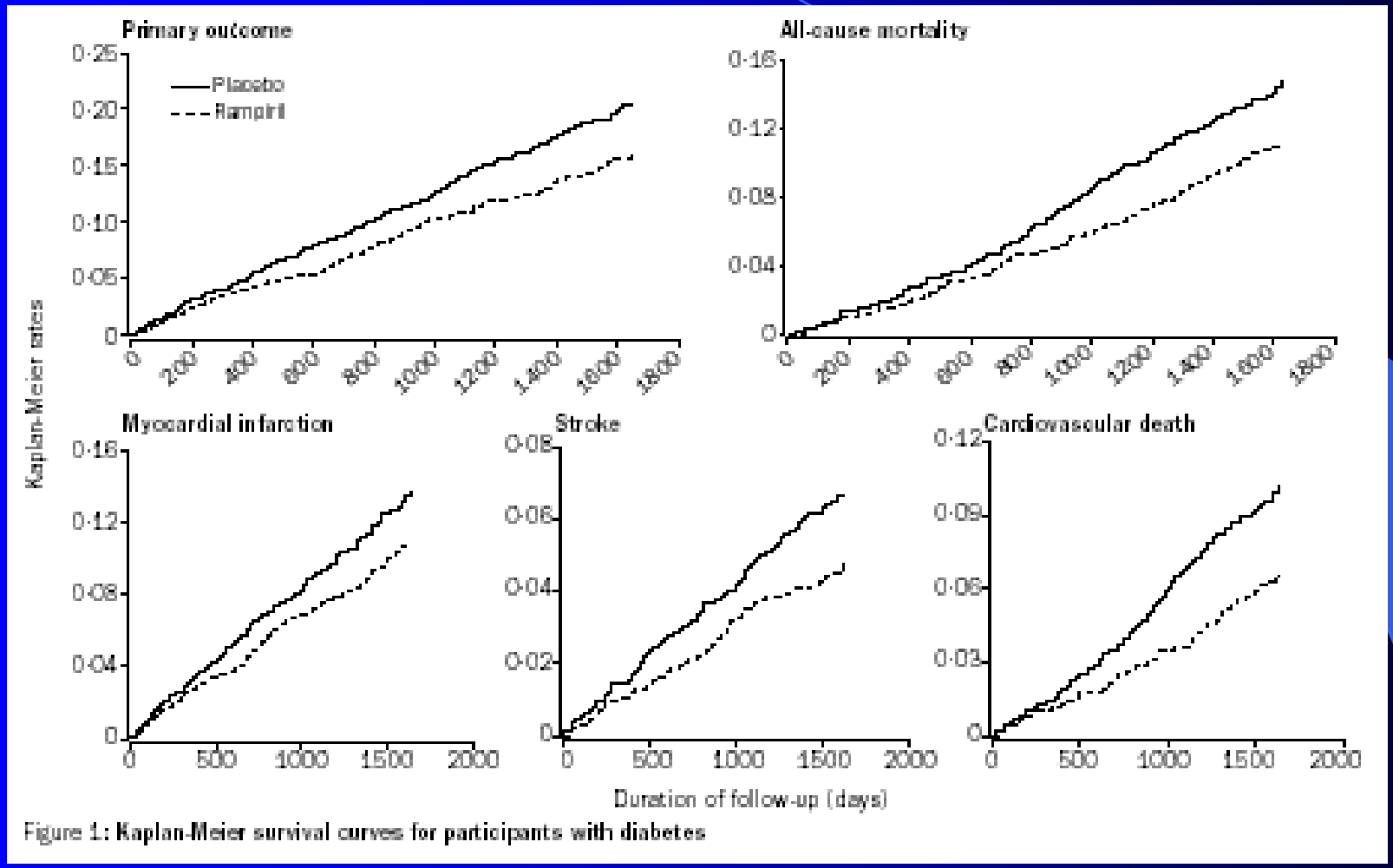


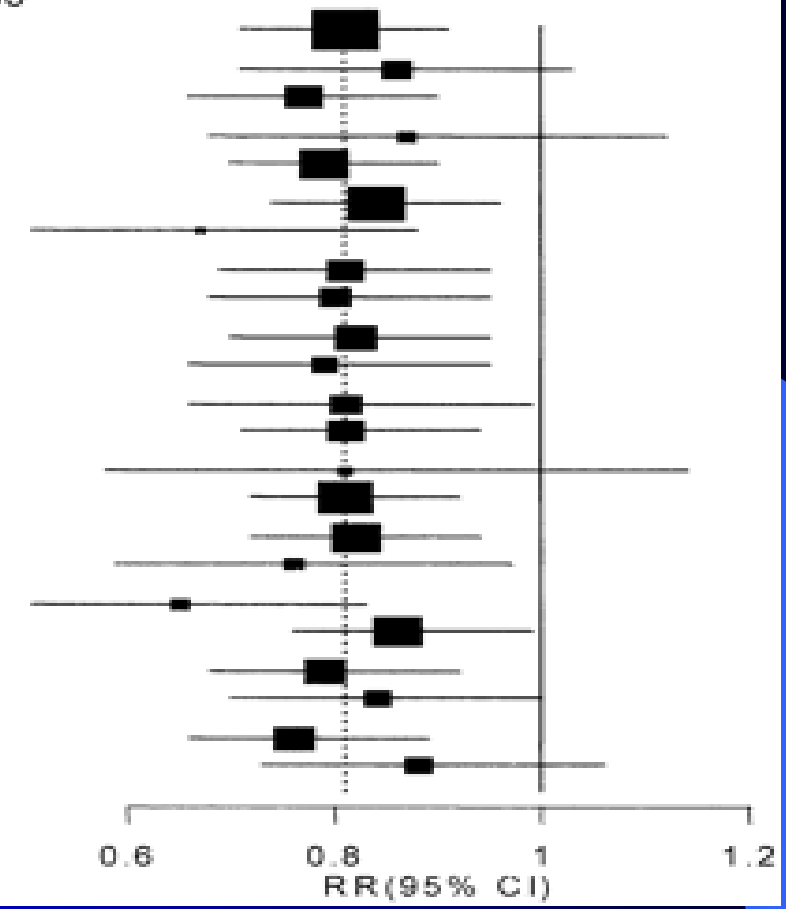
Figure 1: Kaplan-Meier survival curves for participants with diabetes

p=0.01 **p=0.0074** **p=0.0001**

HOPE and MICRO-HOPE Study. **Lancet 2000;355:253-9.**

Effect of Ramipril on Coronary Events in Various Subgroups

Characteristic	No. of Pts	Rate in Placebo
Overall	9297	12.2
Age<65	4169	10.7
Age>=65	5128	13.6
Female	2480	9.4
Male	6817	13.2
Smoker-	7977	11.5
Smoker+	1319	16.5
Hypertension-	4942	11.8
Hypertension+	4355	12.8
Diabetes-	5720	11.8
Diabetes+	3577	13.0
Previous-MI-	4402	8.7
Previous-MI+	4892	15.4
CHD-	1820	7.5
CHD+	7477	13.3
Lipid lowering drug-	6639	13.1
Lipid lowering drug+	2658	10.2
ASA-	2484	12.1
ASA+	6813	12.3
Betablockers-	5624	12.2
Betablockers+	3673	12.4
Previous-PTCA/CABG-	5614	12.7
Previous-PTCA/CABG+	3683	11.6



Circulation 2001;104:522-526.

ACE-Inhibitors and PTCA / Stenting

Variable	OR	95% CI	p Value
ACE-Inhibition	0.46	0.29-0.74	0.001
Debulking	4.56	1.77-11.70	0.001
No of diseased vessels	1.44/vessel	1.12-1.87	0.005
Restenotic lesion	1.78	1.18-2.68	0.006
Prior CABG	0.65	0.41-1.00	0.051
Lesion length	1.02/mm	1.00-1.04	0.052

Ellis et al. Am J Cardiol 2002;89:937-40.

ACE-Inhibitor Therapy

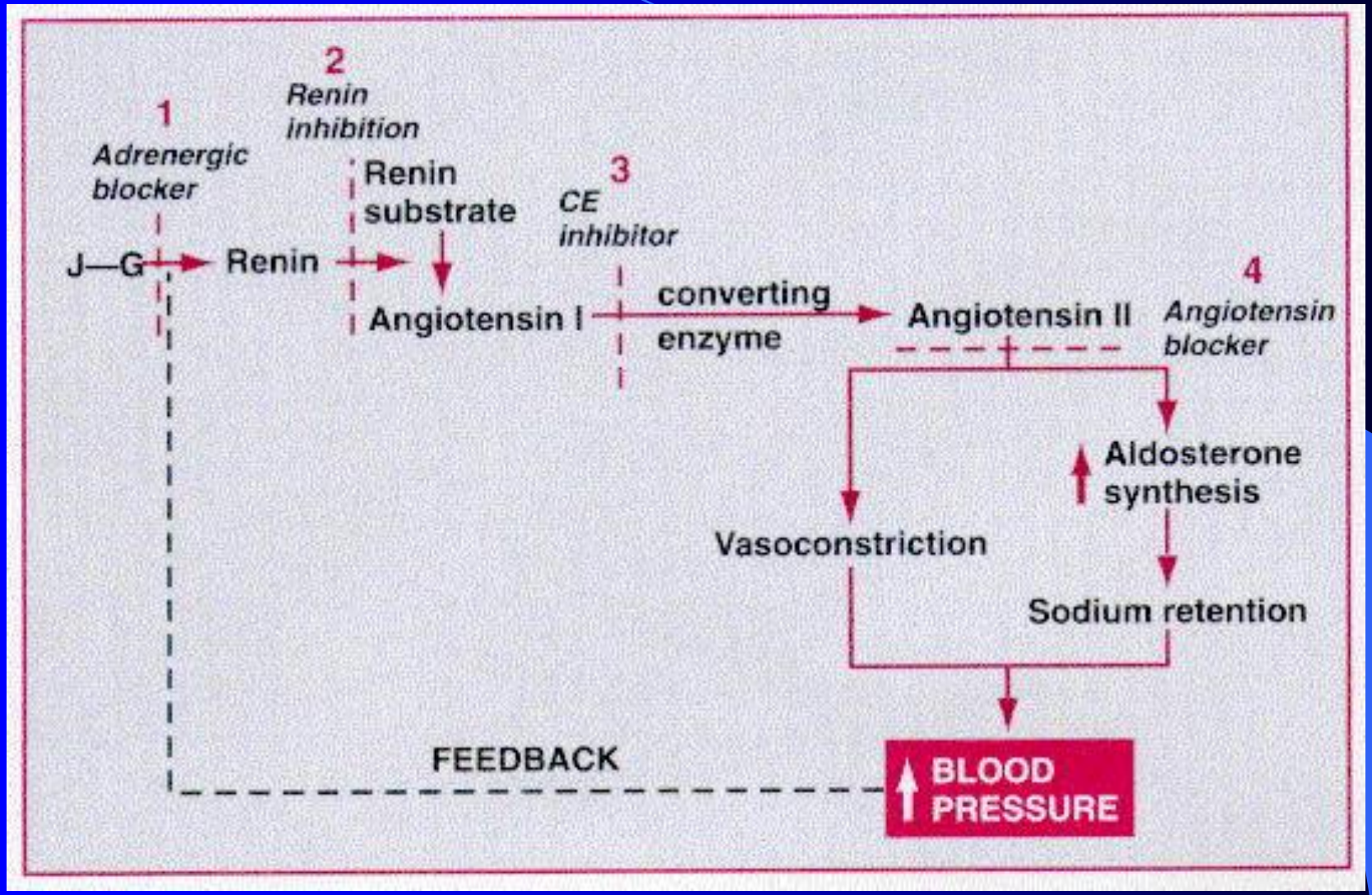
- CAD without contraindications to ACE-I
- CAD with SBP ≥130 mm Hg
- Type II DM with or without CAD
- Insulin resistance with SBP ≥130 mm Hg
- CHF and/or LV dysfunction

O' Keefe et al. J Am Coll Cardiol 2001;37:1-8.

Objectives

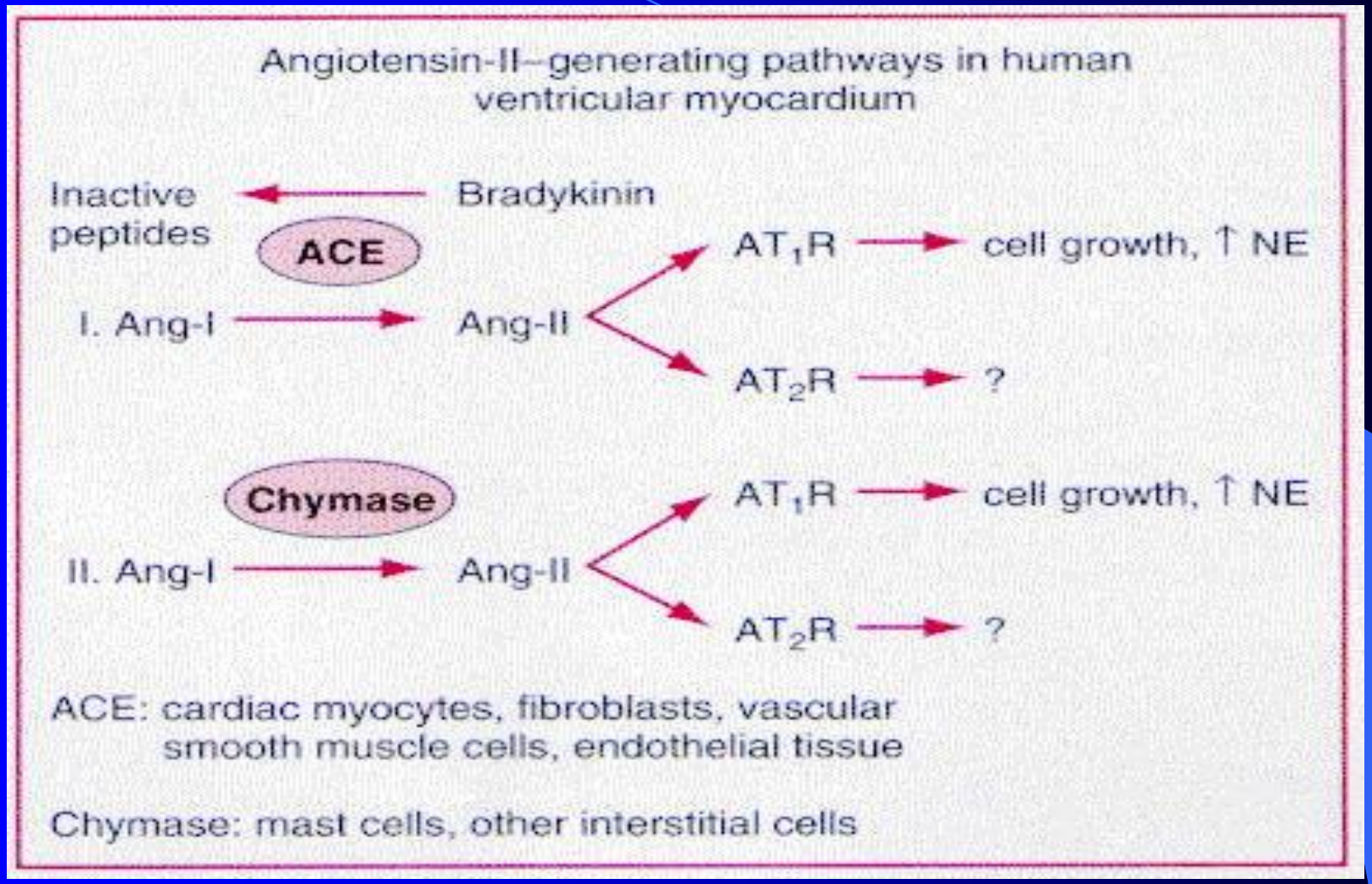
- Impact of ACE-Inhibitors on atherosclerotic heart disease
- **ACE-Inhibitors and coronary microcirculation**
- Anti-ischemic effect of ACE-Inhibitors in patients with risk factors for CAD or documented CAD
- Future directions - ACE genotyping

ACE-I Pharmacology (I)



The four sites of action of inhibitors of the renin-angiotensin system. J-G: Juxtaglomerular apparatus; CE: Converting Enzyme. **Kaplan NM: Clinical Hypertension 1998.**

ACE-I Pharmacology (II)

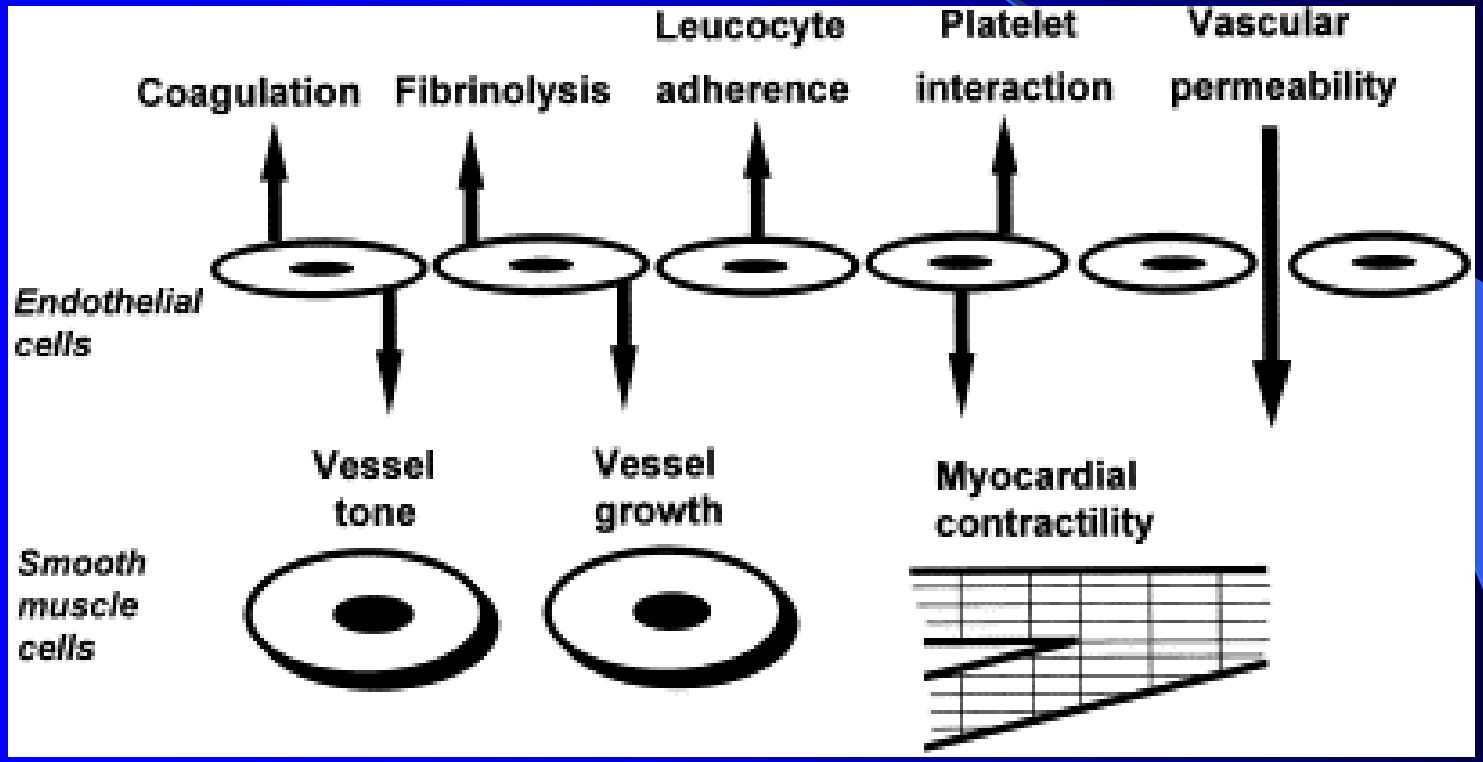


Pathways of angiotensin II formation (AT_1R= Type 1 Receptor, NE = Norepinephrine). **M Bristow in: Braunwald – Zipes – Libby eds. Heart Disease 2001, Ch 18, 562-599.**

A-II, BK: Effect on vascular endothelium

↑ t-PA (BK) ↑ ICAM-1 (A-II)

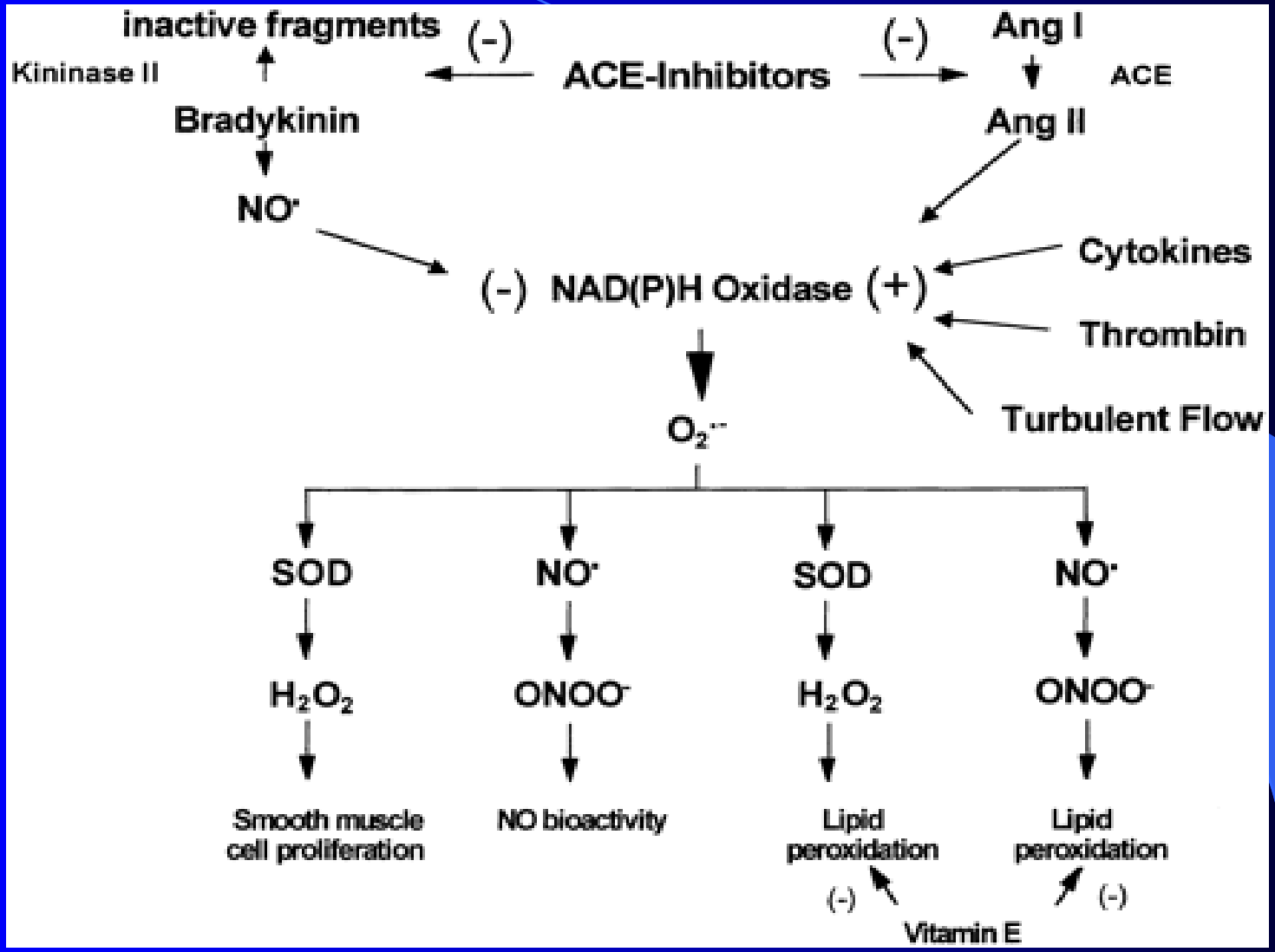
thrombin ↑ PAI-1 (A-II) ↑ VCAM-1 (A-II) ↓ Prostacyclin (A-II)



Vasodilation (ACE-I, BK): NO (↑), Prostacyclin (↑), EDHF (↑); **Vasoconstriction**: A-II (AT1), ET-1

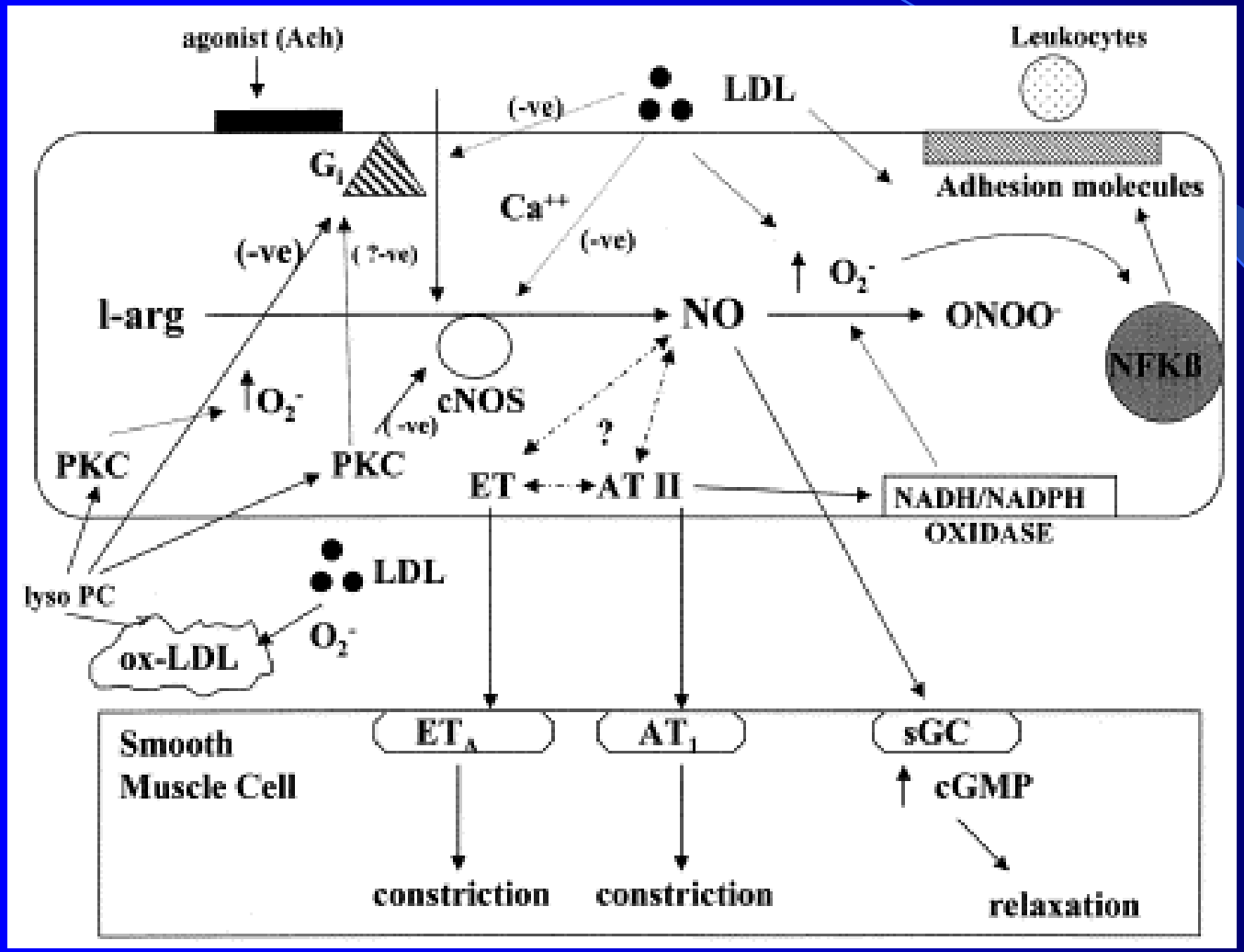
J Am Coll Cardiol 1997;30:325-33 (Modified).

ACE-I Action and Vascular Oxidative Stress



Circulation 2001;104:1571-1574.

Oxidative Stress leads to attenuation of endothelium-dependent vasodilation



Mechanisms: 1) decreased production of NO through oxidized LDL-mediated mechanisms, and by 2) increased destruction of NO by superoxide. G_i = pertussis sensitive G protein; O_2^- = superoxide anion; ONOO$^-$ = peroxynitrite anion; PKC = protein kinase C; cNOS = constitutive form of nitric oxide synthase; ET = endothelin; AT II = angiotensin II; ox-LDL = oxidized LDL; lyso PC = lysophosphatidylcholine; sGC = soluble guanylate cyclase; cGMP = cyclic guanosine monophosphate; NFKB = nuclear factor kappa beta

J Am Coll Cardiol 1999;34:631-8.

Why should we study the coronary microcirculation? (I)

- Even the most seminal reactions, autoregulation and metabolic dilatation, are incompletely understood
- CAD is not only an epicardial vessel disease
- There is great difficulty in the clinical evaluation of coronary microcirculation. Remember Syndrome X?
- Animal and human data suggest that dysfunction of coronary microcirculation can produce cardiac abnormalities. (e.g data with coronary infusion of ET1, data with measurement of CFR following PTCA)

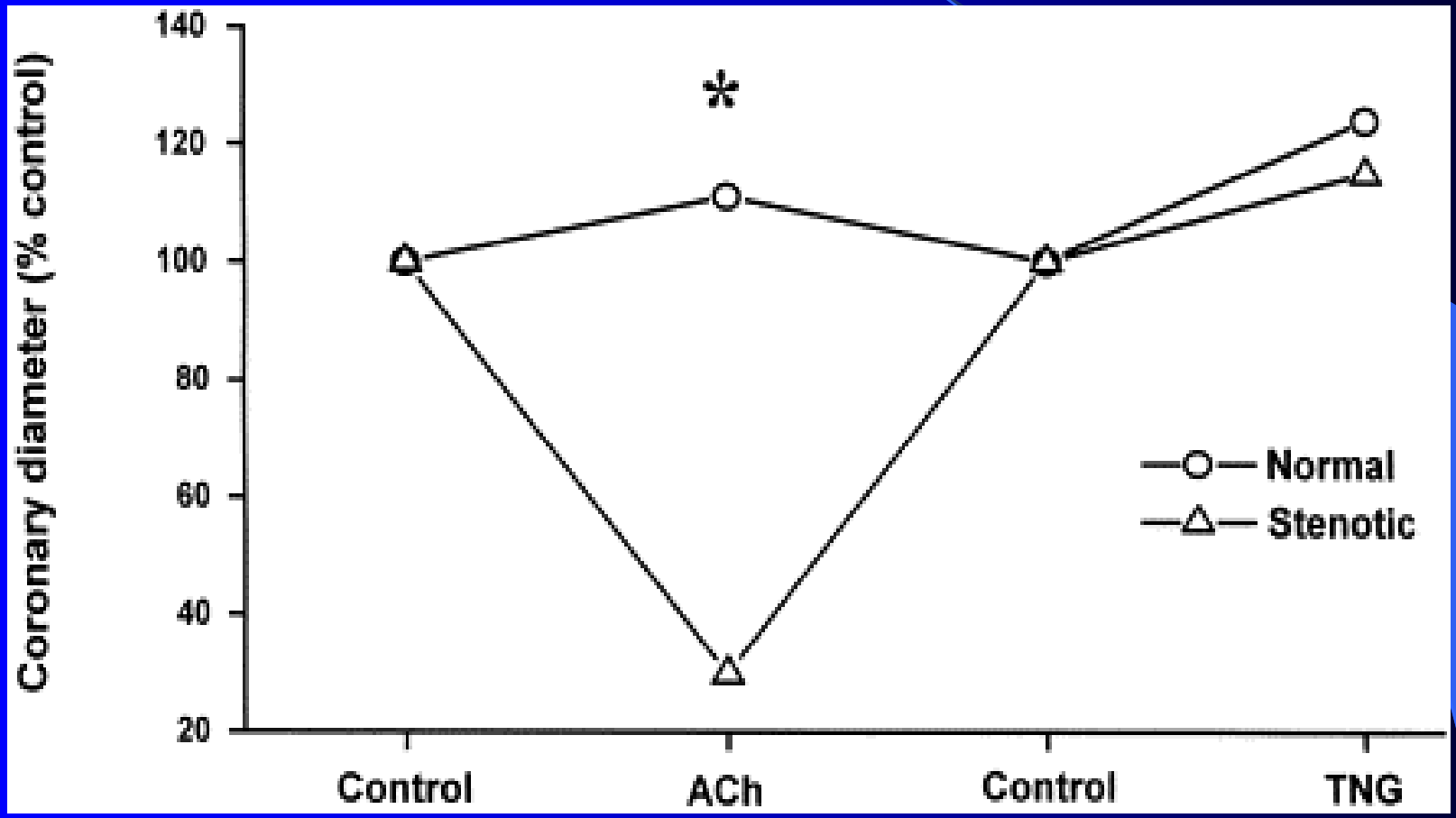
Am J Physiol Heart Circ Physiol 2000;279:H2581-84.

Why should we study the coronary microcirculation? (II)

- Identification of patients with paradoxical vasoconstriction during increases in O_2 consumption
- Assess efficacy of various pharmacologic interventions who aim to produce dilation of coronary microcirculation
- Administration of drugs that “target” the coronary circulation can improve outcomes of interventional techniques (PTCA, Stenting)

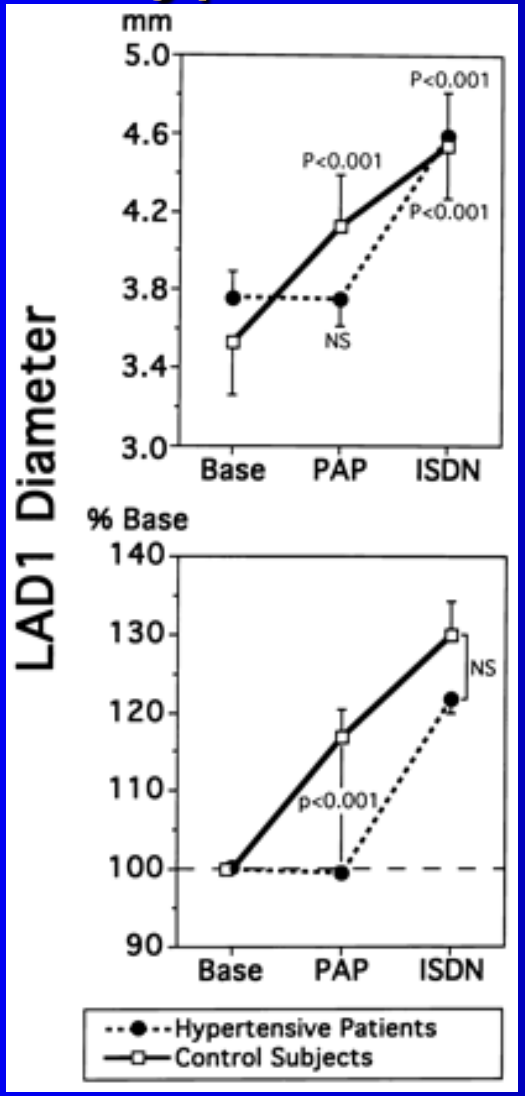
Am J Physiol Heart Circ Physiol 2000;279:H2581-84.

Paradoxical Vasoconstriction induced by Acetylcholine in atherosclerotic coronary arteries



Ludmer et al. N Engl J Med 1986;315:1046-51.

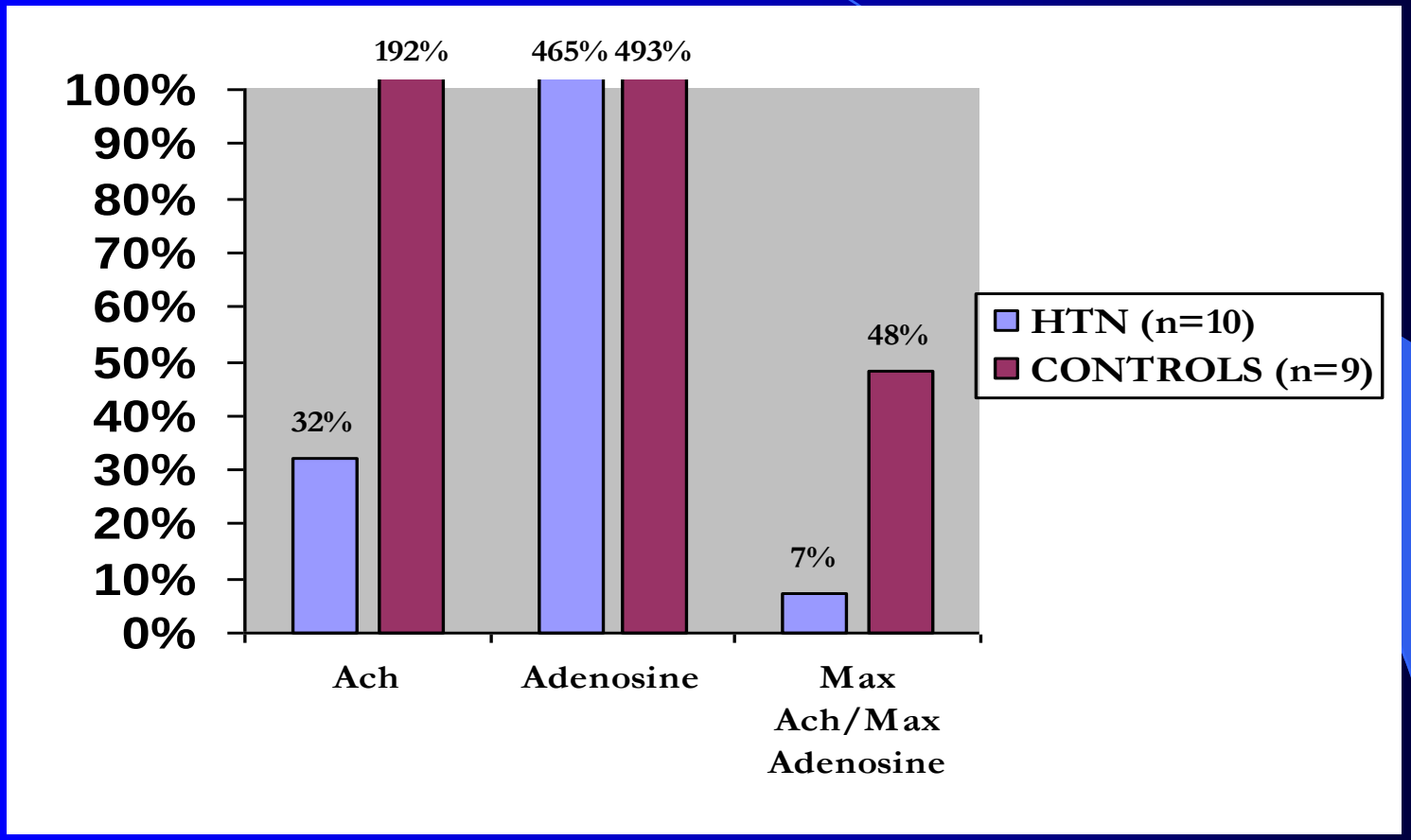
Loss of flow-dependent coronary artery dilation in patients with hypertension and normal coronaries



LAD1: Proximal LAD diameter measured at *base*, after *PAP*, and after *ISDN*. The increase in flow (*PAP*) causes a significant dilation in controls (n=10, 17% ± 3 %) compared to HTN subjects (n=14, -0.4% ± -0.6%).

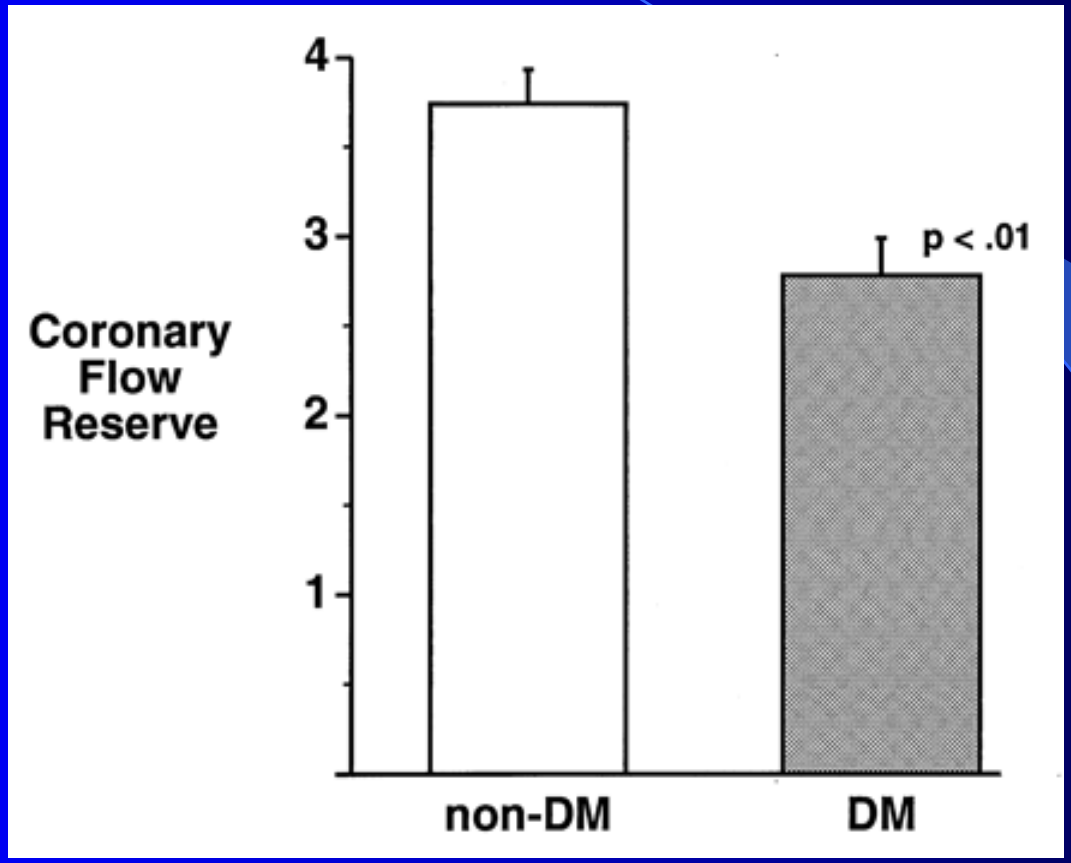
Antony I. et al. Circulation 1995;91:1624-1628.

Impaired endothelium-mediated relaxation in human coronary *resistance* arteries



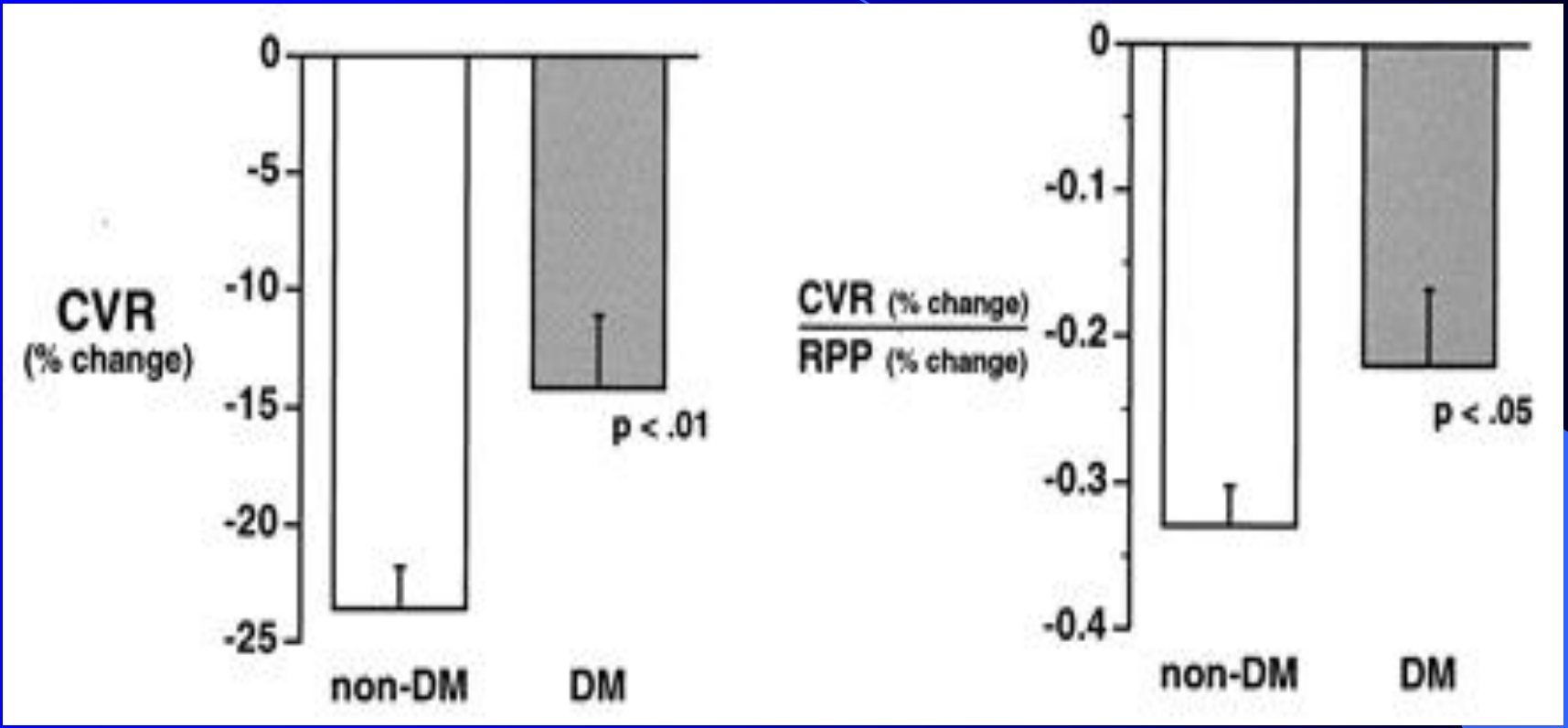
Mean CBF measurements in patients with HTN-LVH compared to controls after infusion of Ach and Adenosine. **Treasure CB et al. Circulation 1993;87:86-93.**

Coronary microvascular dysfunction in patients with Diabetes (CFR)



Bar graph of maximal pharmacologic (papaverine or adenosine) coronary blood flow reserve in patients with diabetes mellitus (DM) (2.8±0.2, n=19) and non-diabetics (non-DM) (3.7±0.2, n=22). **Nasher P. et al. Circulation 1995;91:635-40.**

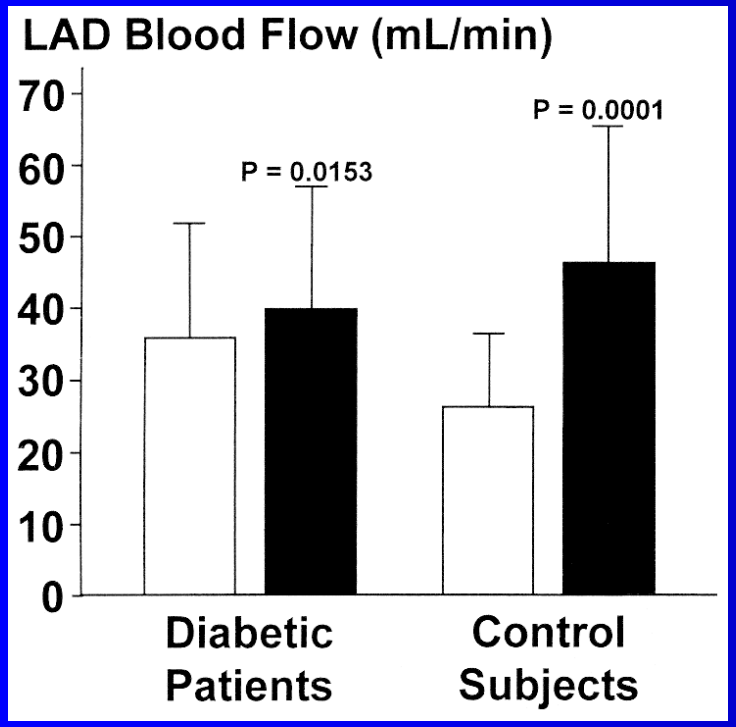
Coronary microvascular dysfunction in patients with Diabetes (CVR)

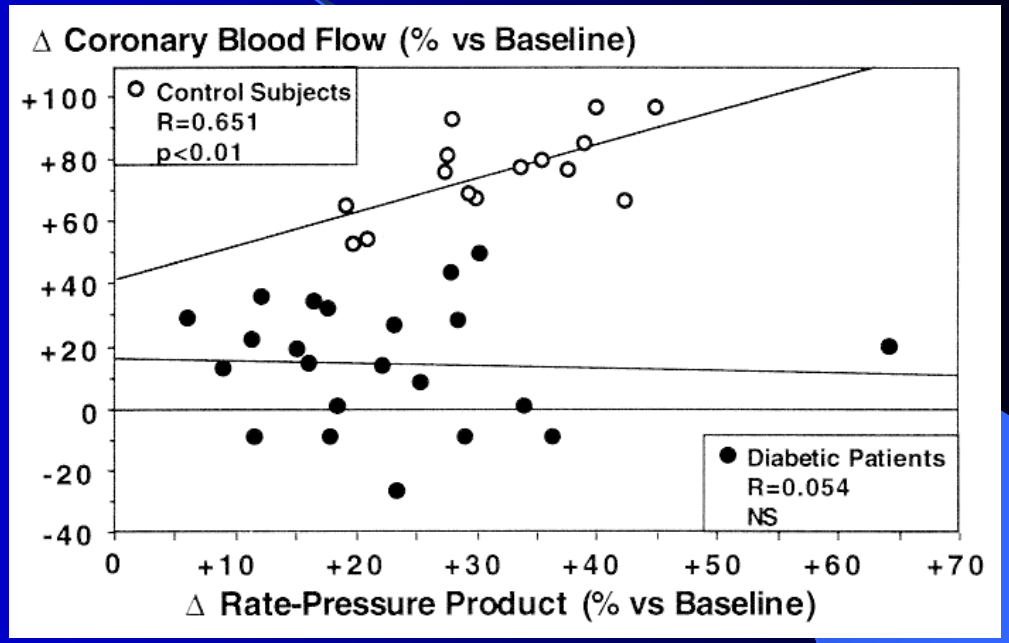


Bar graphs of change in coronary vascular resistance (CVR) and coronary vascular resistance *normalized* to the increase in rate-pressure product (RPP) during atrial pacing stress in patients with diabetes mellitus (DM) (↓14% ± 3%) and non-diabetics (non-DM) (↓24% ± 2%). **Nasher P. et al. Circulation 1995;91:635-40.**

Impairment of coronary microvascular dilation during CPT in Type II DM and abnormal ^{201}TI Imaging

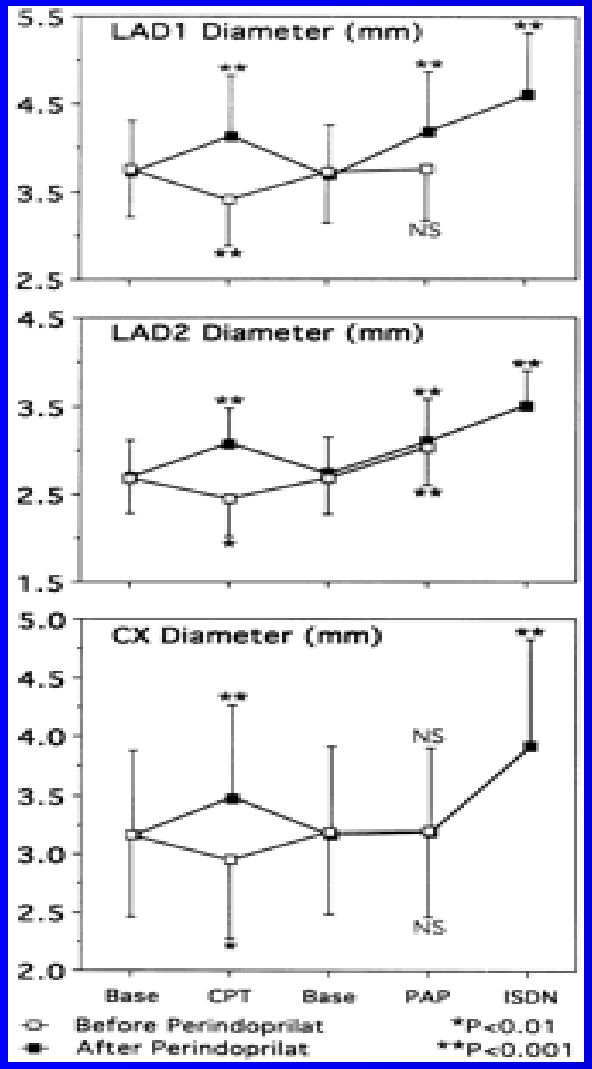
↑ 14.7±19.8% ↑ 75.5±13.5%

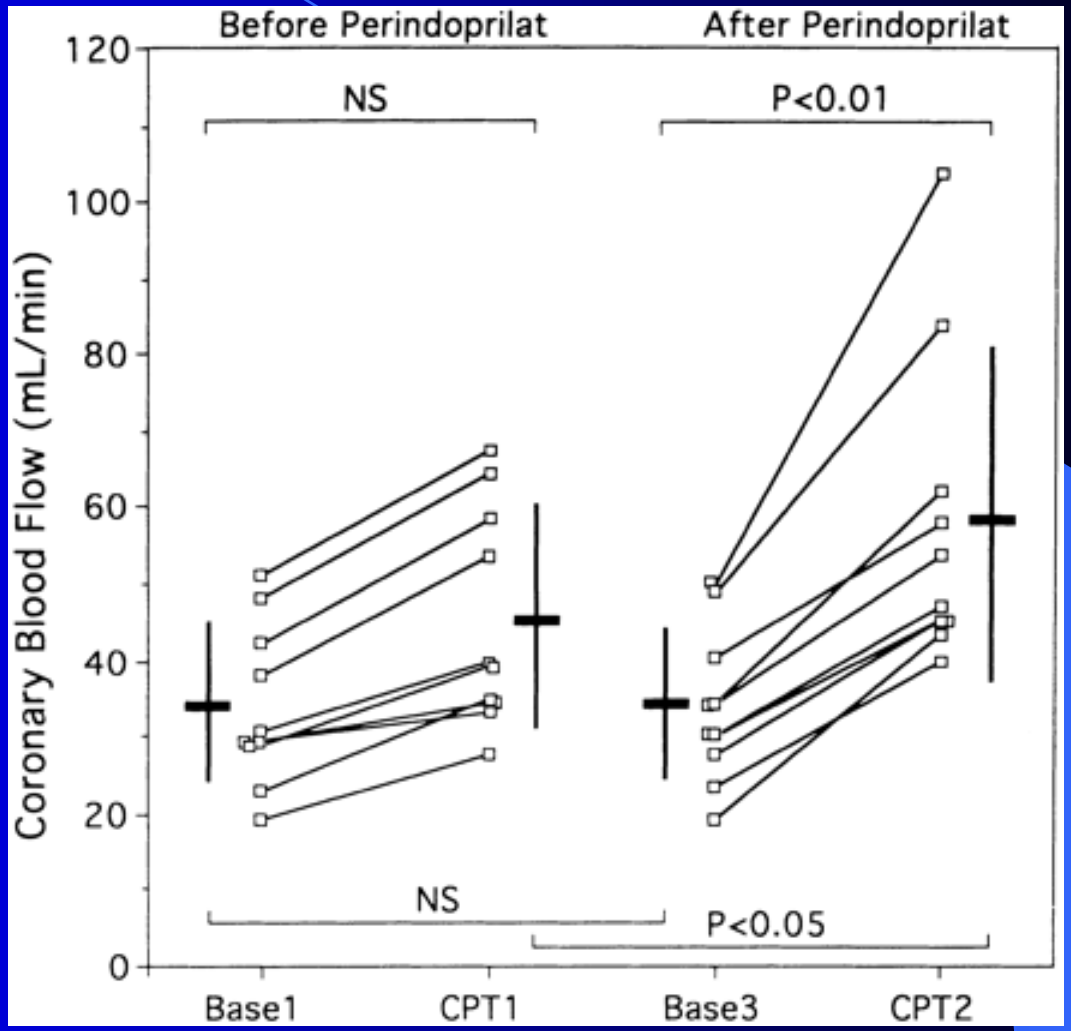




(**Left**): Coronary blood flow in LAD in the two groups of patients at *baseline [white square]* and during the *CPT [black square]*. (**Right**) Relationship between changes in left anterior descending coronary blood flow and in the rate-pressure product induced by the CPT in the two groups of patients. There was a significant correlation between the two parameters in only the control subjects. **Nitenberg A et al. Diabetes 2001;50(5):1180-85.**

ACE-I restores flow-dependent and CPT-induced dilations in coronary arteries of hypertensive patients

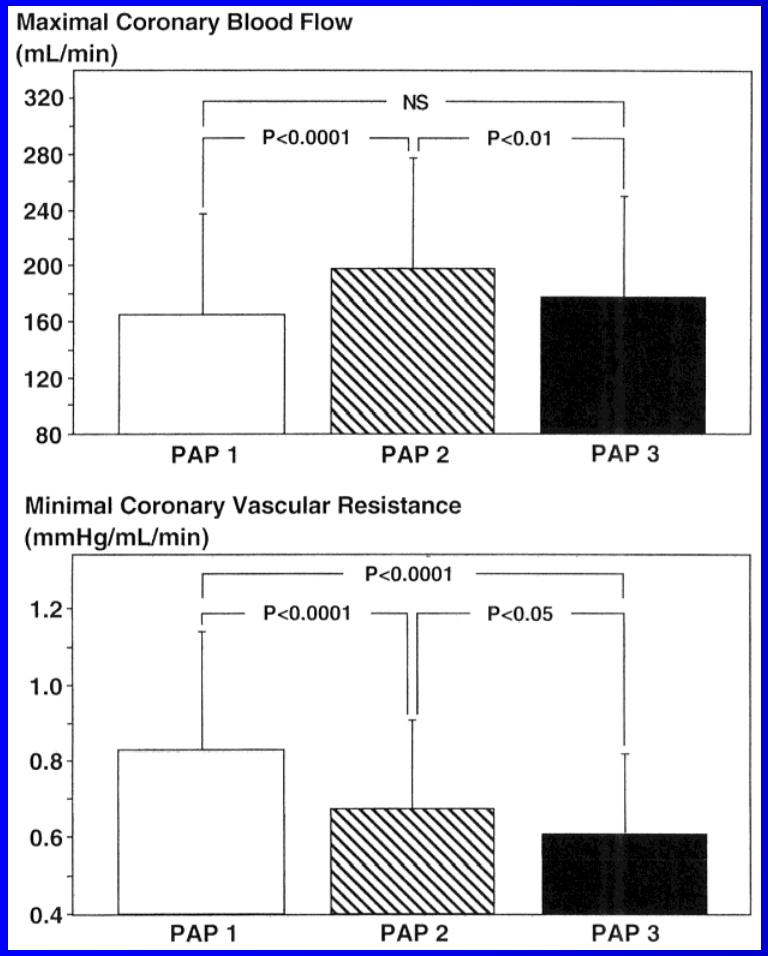




Antony I, et al. Circulation 1996;94:3115-3122.

ACE-I improve CBF: Epicardial coronary arteries are more than conductance vessels

163±73 197 ±80 178 ±72

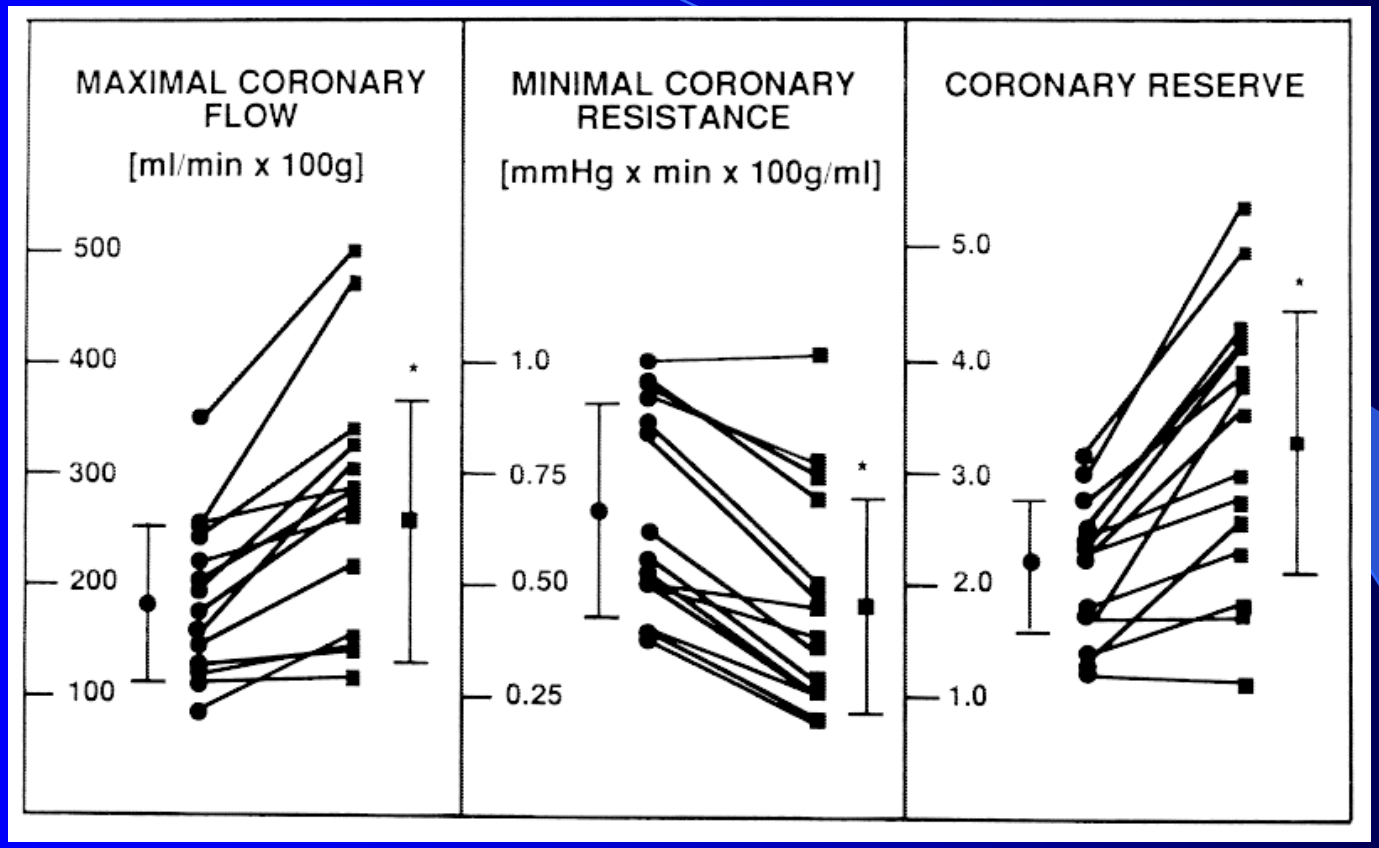


0.8 ±0.3 0.7 ±0.2 0.6 ±0.2

J Cardiovasc Pharmacol 2000;36:570-576.

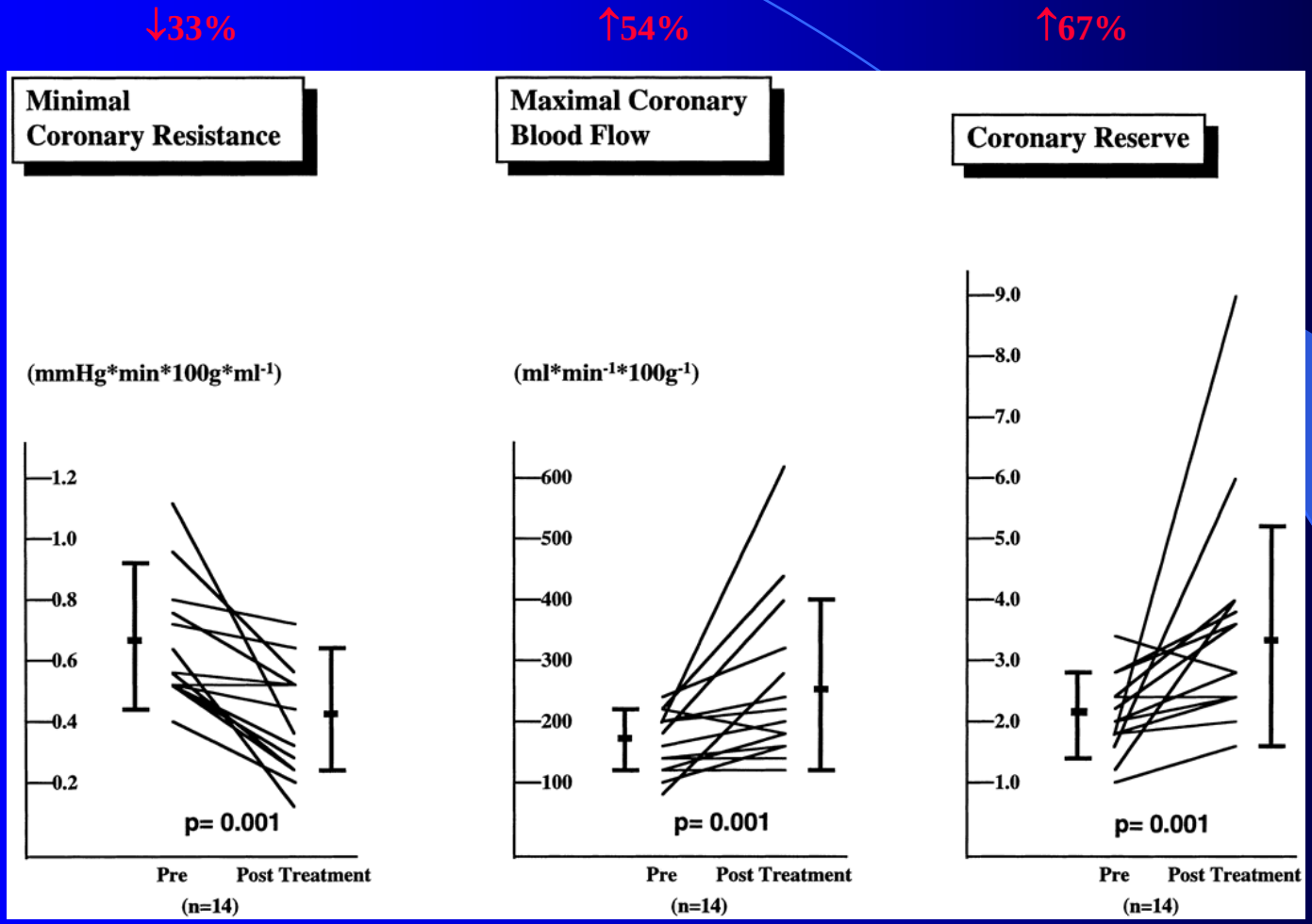
Maximal coronary blood flow and minimal coronary vascular resistance measured in the distal left anterior descending coronary artery after intracoronary papaverine (PAP), before (PAP 1) and after (PAP 2) administration of perindoprilat, and after papaverine after intracoronary isosorbide dinitrate (PAP 3). Note the increase in flow (PAP2) is more compared to the decrease of vascular resistance (PAP3<PAP2).

CFR after long-term treatment with Enalapril



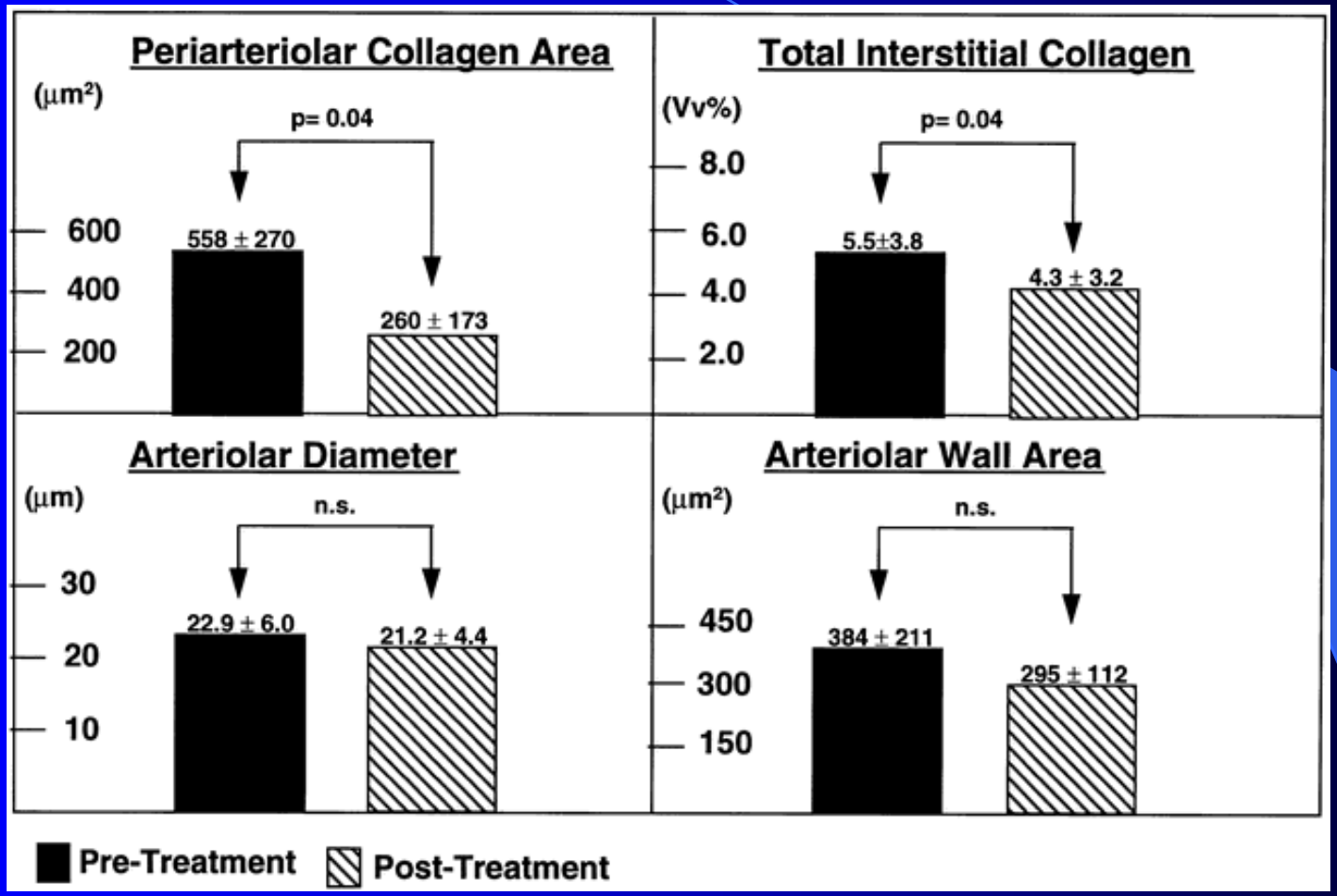
Effects of long-term ACE-I treatment on coronary vasodilating capacity. Significant increase in maximal coronary flow and decrease in minimal coronary resistance occurred in response to dipyridamole (0.5 mg/kg body wt IV), with a corresponding increase in coronary reserve. Minimal coronary resistance did not change in only one patient. Mean ± SD is shown. (***Closed circle*** indicates before treatment; ***closed square***, after treatment. *P < .001. **Hypertension 1996;27:1031-38.**

Repair of coronary arterioles after treatment with Perindopril in Hypertensive Heart Disease (I)



Individual changes in coronary hemodynamics before and after long-term ACE-I therapy (12 months). **Schwaartzkopff B, et al. Hypertension 2000;36:220-225.**

Repair of coronary arterioles after treatment with Perindopril in Hypertensive Heart Disease (II)



Morphological changes before and after therapy. Evidence for regression of periarteriolar collagen. **Hypertension, 2000;36:220-225.**

Summary: Effects of ACE-I on coronary vasomotion in Hypertensive patients

- Coronary vasodilator responses to pharmacological (Ach) and physiological (CPT, Pacing) stimuli are impaired in the presence of endothelial dysfunction
- Both animal and human studies have demonstrated that ACE-I (acute and chronic treatment) may reverse abnormal vasomotion
- ? Exact role of NO, BK, EDHF, free radicals.

Eur Heart J 1998;19:(Suppl J):J45-J51.

Vascular Biology

Abnormal Flow-Mediated Epicardial Vasomotion in Human Coronary Arteries Is Improved by Angiotensin-Converting Enzyme Inhibition

A Potential Role of Bradykinin

Abhiram Prasad, MB, MRCP, Syed Hussain, MD, Arshed A. Quyyumi, MD, MRCP, FACC
Bethesda, Maryland

Methods-Protocol: In 19 patients with mild atherosclerosis, metabolic vasodilation was assessed during cardiac pacing. Pacing was repeated during separate intracoronary infusions of low-dose BK and enalaprilat. Endothelium-dependent and endothelium-independent vasodilation was estimated with intracoronary BK and sodium nitroprusside respectively.

J Am Coll Cardiol 1999;33:794-804.

Enalaprilat induces endothelium-dependent coronary artery dilation

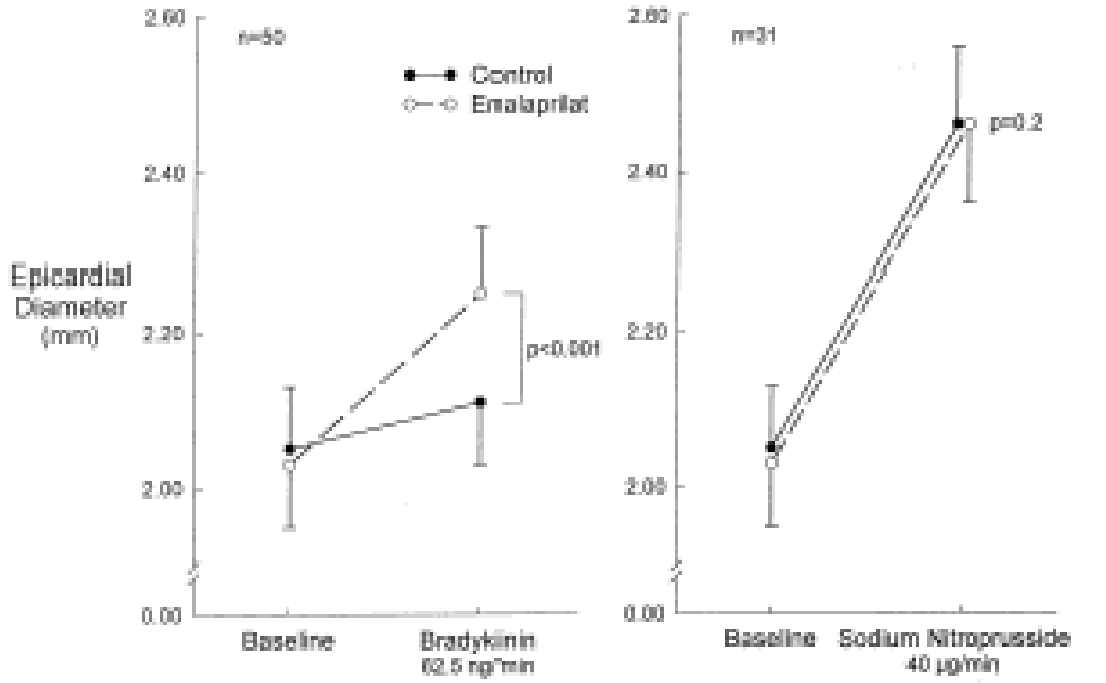


Figure 1. Effects of bradykinin **(left)** and sodium nitroprusside **(right)** before **(control, •)** and after enalaprilat (○) on epicardial diameter. (Data represent mean ± SEM).

J Am Coll Cardiol 1999;33:794-804.

Enalaprilat reverses vasoconstriction in segments with endothelial dysfunction after rapid atrial pacing

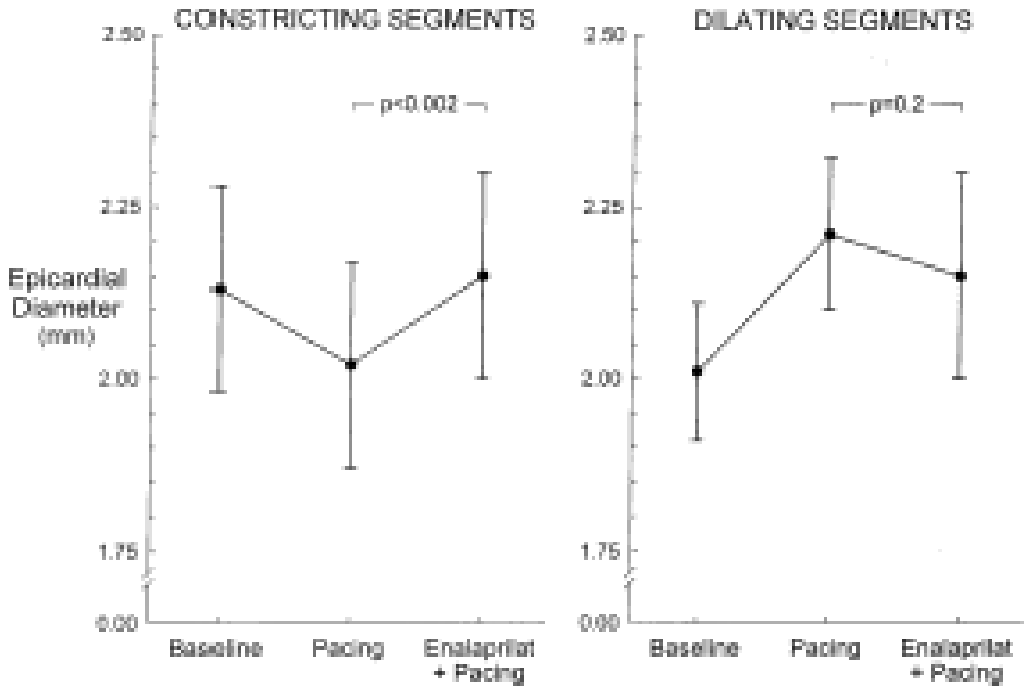


Figure 2. The effects of cardiac pacing before and after enalaprilat on coronary epicardial segments that initially constricted (**left**, n = 20) or dilated (**right**, n = 30) with cardiac pacing. There was no significant difference (p = 0.5) between the mean baseline diameters of constricting segments (2.1 ± 0.1 mm) compared to dilating segments (2.0 ± 0.1 mm). Data represent mean ± SEM.

J Am Coll Cardiol 1999;33:794-804.

BK effect similar to Enalaprilat effect

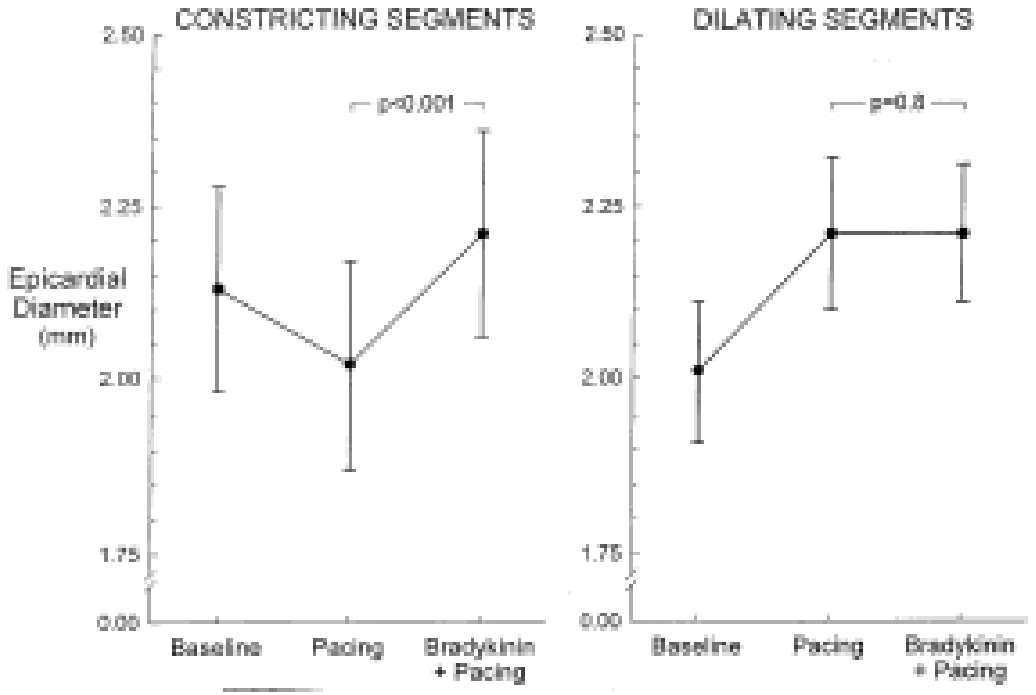


Figure 4. The effects of cardiac pacing before and after 62.5 ng/min of intracoronary bradykinin on coronary epicardial segments which constricted **(left)** or dilated **(right)** with control pacing. Data represent mean ± SEM.

J Am Coll Cardiol 1999;33:794-804.

Journal of the American College of Cardiology
© 2000 by the American College of Cardiology
Published by Elsevier Science Inc.

Vol. 36, No. 5, 2000
ISSN 0735-1097/00/$20.00
PII S0735-1097(00)00892-5

Contribution of Bradykinin Receptor Dysfunction to Abnormal Coronary Vasomotion in Humans

Abhiram Prasad, MBBS, MRCP, Syed Husain, MD, William Schenke, BS, Rita Mincemoyer, RN, Neal Epstein, MD, Arshed A. Quyyumi, MD, FRCP, FACC

Bethesda, Maryland

Methods - Protocol: In 53 patients with atherosclerosis or its risk factors and 9 controls, endothelium-dependent vasomotion was assessed with Ach and BK and endothelium-independent function with sodium nitroprusside. Correlation with serum ACE levels was performed.

J Am Coll Cardiol 2000;36:1467-73.

Coronary Vascular resistance response to Ach and Nipride

p=0.025 **p=0.1 (NS)**

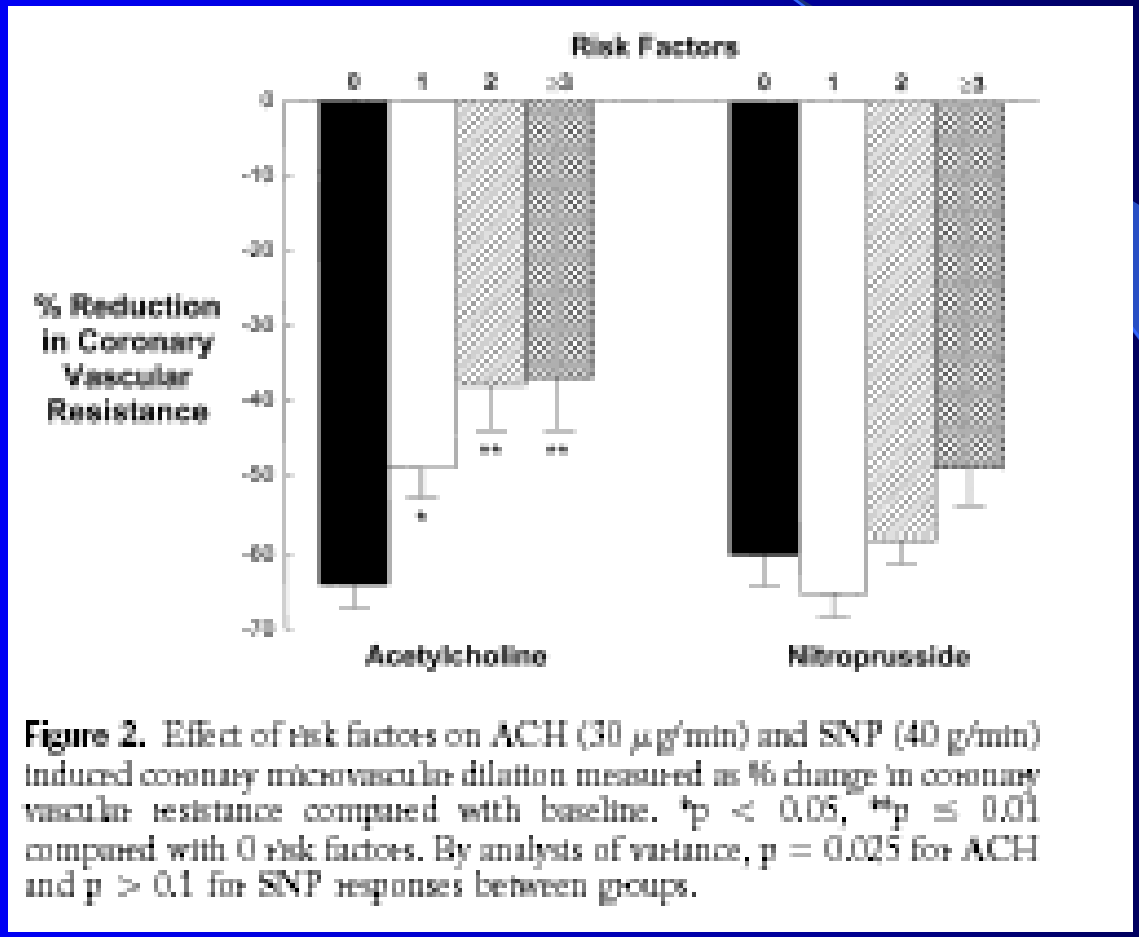


Figure 2. Effect of risk factors on ACH (30 μg/min) and SNP (40 g/min) induced coronary microvascular dilation measured as % change in coronary vascular resistance compared with baseline. *p < 0.05, **p ≤ 0.01 compared with 0 risk factors. By analysis of variance, p = 0.025 for ACH and p > 0.1 for SNP responses between groups.

J Am Coll Cardiol 2000;36:1467-73.

BK mediated vasodilation is similar irrespective of risk factors

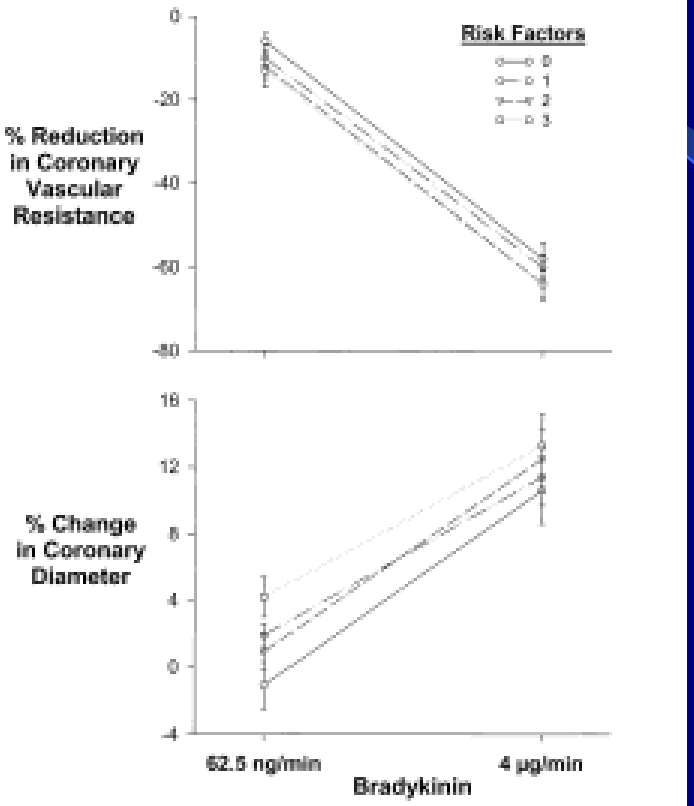


Figure 3. Effect of risk factors on bradykinin-induced coronary epicardial dilation (measured as % change in diameter) and microvascular dilation (measured as % change in resistance). No difference in responses between risk groups by analysis of variance.

p=0.5

J Am Coll Cardiol 2000;36:1467-73.

BK induced vasomotion is adversely affected by ↑ ACE levels and DD genotyping

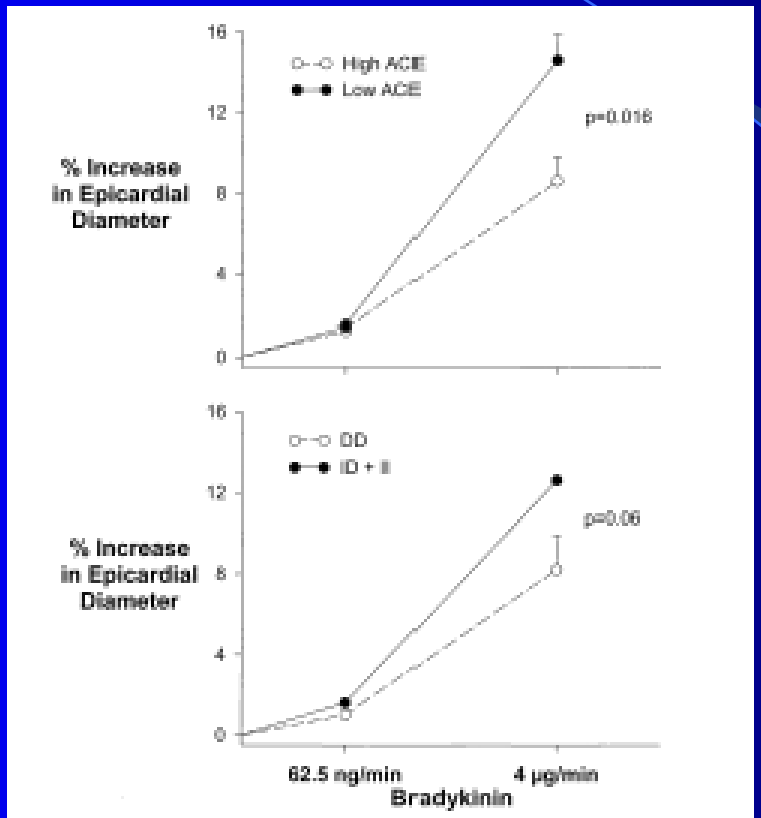


Figure 6. (Top panel) Bradykinin-mediated epicardial vasomotion in patients with serum ACE levels > median value of 9.9 U/ml (high ACE, n = 30) compared with those with levels below median (low ACE, n = 32). **(Lower panel)** Bradykinin-mediated epicardial vasomotion in patients with DD (n = 13) genotype compared with patients with the ID or II genotypes (n = 49). The comparison between groups by analysis of variance. ACE = angiotensin-converting enzyme.

J Am Coll Cardiol 2000;36:1467-73.

Conclusions

- The kallikrein-kinin system plays a major role in the regulation of resting tone and flow-mediated epicardial vasodilation.
- Endothelial dysfunction in atherosclerosis appears to be receptor specific, involving the muscarinic receptor with relative sparing of the kinin receptor pathway
- BK activity appears to be influenced by serum ACE levels and the ACE I/D genotype.
- ACE-I and Neutral endopeptidase inhibitors enhance endogenous BK activity and may reverse endothelial dysfunction.

Objectives

- Impact of ACE-Inhibitors on atherosclerotic heart disease
- ACE-Inhibitors and coronary microcirculation
- **Anti-ischemic effect of ACE-Inhibitors in patients with risk factors for CAD or documented CAD**
- Future directions - ACE genotyping

Clinical Importance: Improvement of Myocardial Blood Flow to ischemic regions by ACE-I with Quinaprilat IV

- Myocardial Blood Flow was analyzed in ischemic and non-ischemic regions of 10 symptomatic patients with CAD using repetitive [^{15}O] water PET at rest and during maximal dobutamine stress before and after ACE inhibition with quinaprilat 10 mg IV. 8 patients underwent the same protocol without quinaprilat
- Rate-pressure product was comparable in both groups
- Changes in MBF and total coronary resistance were examined noninvasively in patients before and after ACE-I

Schneider C et al. J Am Coll Cardiol 1999;34:1005-11.

IV Quinapril increase MBF in ischemic regions

Table 4. Myocardial Blood Flow: Nonischemic Regions

	Placebo		Quinaprilat IV	
(ml/min/g)	Before Placebo	After Placebo	Before Quinaprilat IV	After Quinaprilat IV
Rest	1.13 (0.08; 0.96 to 1.29)	1.27 (0.10; 1.07 to 1.48)	0.93 (0.06; 0.80 to 1.05)	1.23 (0.07; 1.08 to 1.38)‖
Stress	3.19 (0.33; 2.51 to 3.86)*	2.65 (0.29; 2.06 to 3.25)†	2.04 (0.19; 1.67 to 2.42)‡	2.84 (0.35; 2.12 to 3.56)§

Mean (SEM; 95% confidence interval). *$p < 0.0001$ vs. before placebo/rest. †$p < 0.0001$ vs. after placebo/rest. ‡$p < 0.0001$ vs. before quinaprilat IV/rest. §$p < 0.0001$ vs. after quinaprilat IV/rest. ‖$p < 0.003$ vs. before quinaprilat IV/rest.

Table 5. Myocardial Blood Flow: Ischemic Regions

	Placebo		Quinaprilat IV	
(ml/min/g)	Before Placebo	After Placebo	Before Quinaprilat IV	After Quinaprilat IV
Rest	1.34 (0.11; 1.11 to 1.58)	1.40 (0.13; 1.11 to 1.67)	1.29 (0.16; 0.96 to 1.62)	1.27 (0.14; 0.98 to 1.56)
Stress	1.41 (0.17; 1.04 to 1.78)	1.39 (0.19; 0.97 to 1.82)	1.10 (0.13; 0.83 to 1.37)	1.69 (0.17; 1.33 to 2.05)*†

Mean (SEM; 95% confidence interval). *$p < 0.015$ vs. after quinaprilat IV/rest. †$p < 0.015$ vs. before quinaprilat IV/stress.

Schneider C et al. J Am Coll Cardiol 1999;34:1005-11.

IV Quinapril improves Dobutamine Coronary Reserve in ischemic regions

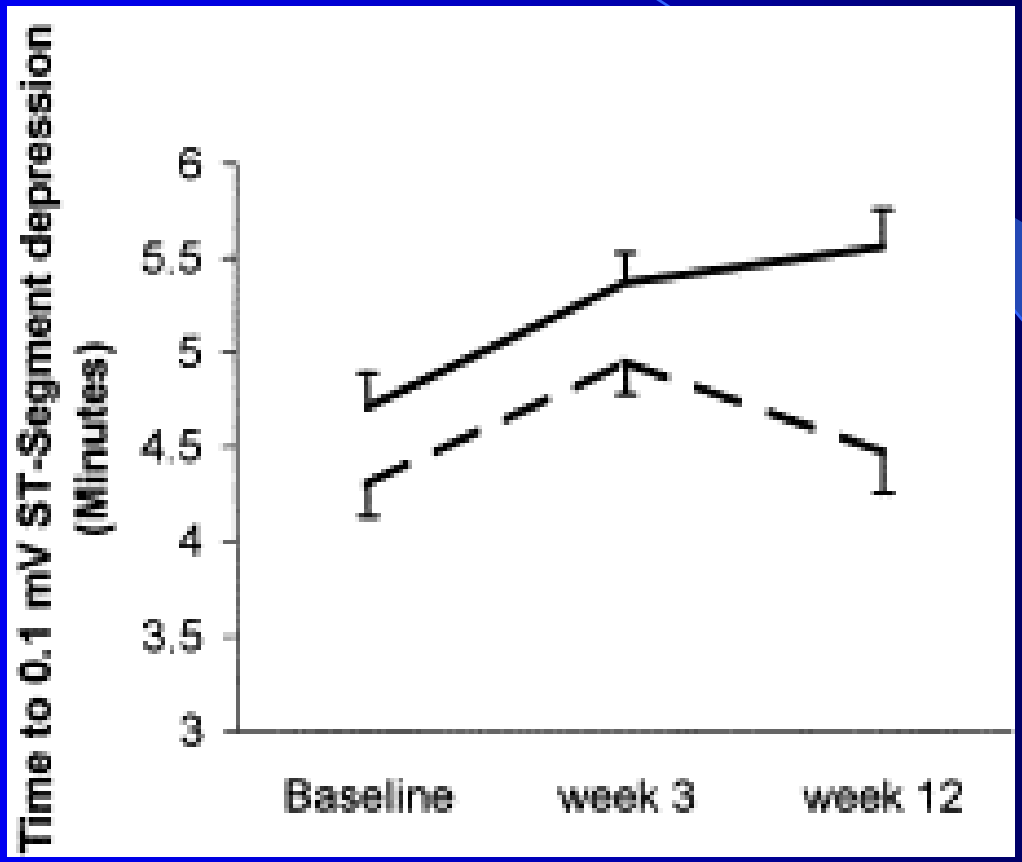
Table 6. Dobutamine Coronary Reserve

	Placebo		Quinaprilat IV	
	Before Placebo	After Placebo	Before Quinaprilat IV	After Quinaprilat IV
Nonischemic regions	3.12 (0.32; 2.47 to 3.77)	2.42 (0.36; 1.70 to 3.15)	2.40 (0.20; 1.99 to 2.81)	2.38 (0.25; 1.87 to 2.89)§
Ischemic regions	1.07 (0.11; 0.8 to 1.32)†‡	1.10 (0.16; 0.76 to 1.45)*	0.97 (0.10; 0.78 to 1.17)‖	1.44 (0.14; 1.14 to 1.75)‡

Mean (SEM; 95% confidence interval). *$p < 0.0001$ vs. nonischemic regions/after placebo. †$p < 0.003$ vs. nonischemic regions/before placebo. ‡$p < 0.002$ vs. ischemic regions/before quinaprilat. §$p < 0.02$ vs. ischemic regions/after quinaprilat. ‖$p < 0.001$ vs. nonischemic regions/before quinaprilat.

Schneider C et al. J Am Coll Cardiol 1999;34:1005-11.

12 weeks of Enalapril reduces exercise-induced myocardial ischemia



Time to 0.1 mV ST-segment depression at baseline, after 3 and 12 weeks treatment with enalapril. Dotted line is placebo group. After 12 weeks the difference between groups is significant (p=0.036). **J Am Coll Cardiol 2001;37:470-4.**

Anti-Ischemic Effects of ACE-I in Hypertension (Duration, RPR)

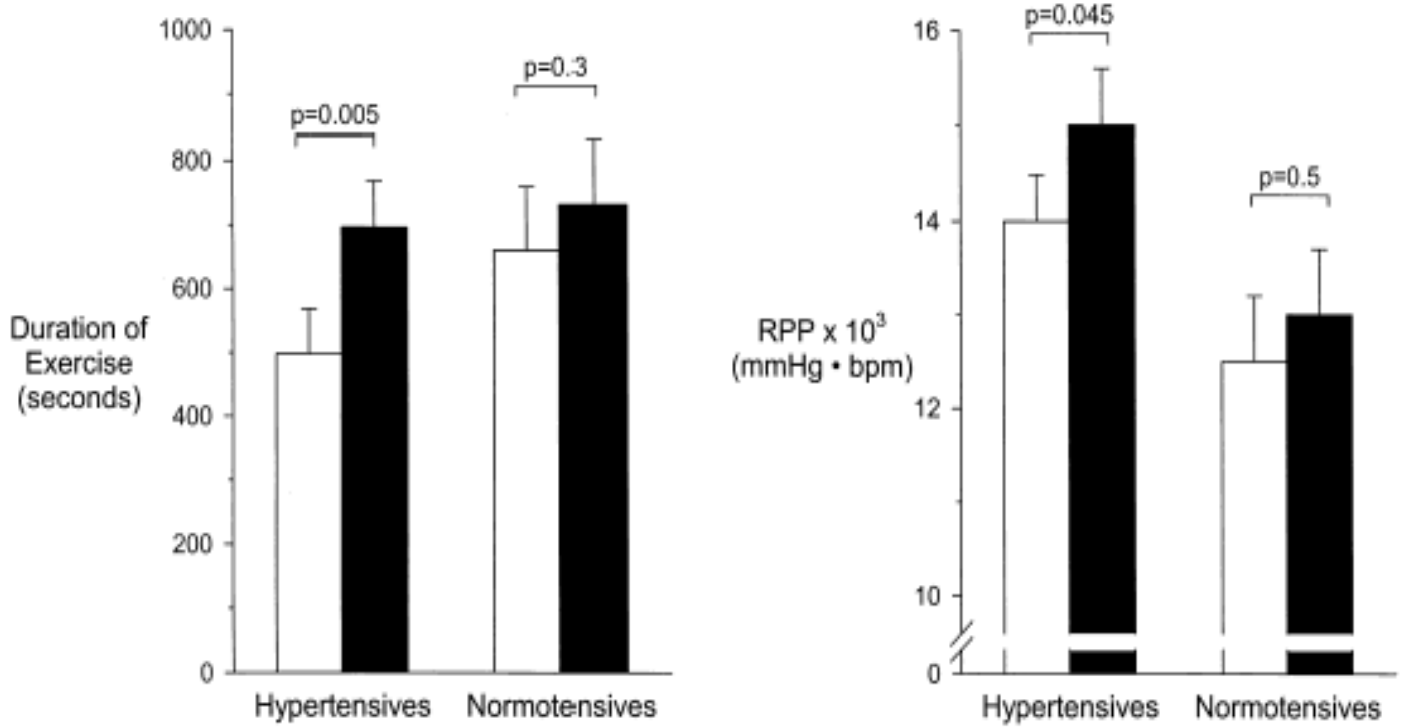


Figure 1. Change in ischemic threshold (rate-pressure product [RPP]) and duration of exercise at the onset of 1-mm ST-depression in hypertensive and normotensive patients before **(open bars)** and after **(solid bars)** treatment with enalapril.

Prasad et al. J Am Coll Cardiol 2001;38:1116-22.

Interpreting Laboratory and Clinical Data

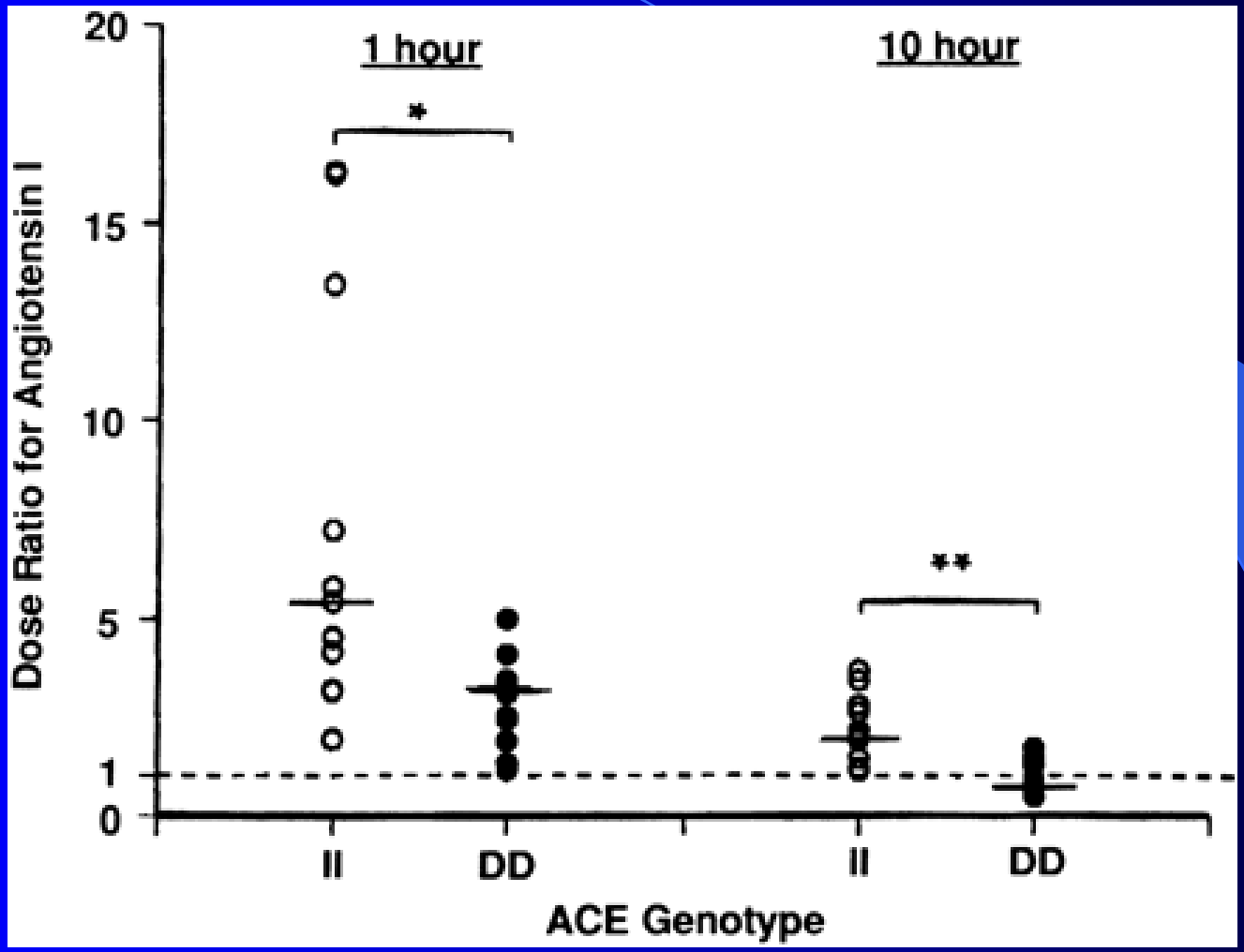
- Although clinical studies failed to demonstrate prevention of the onset of new ischemia[1], data support the antiischemic action of ACE-I on existing ischemia
- The mechanism is double: Reduction of A-II and increase of BK activity

[1]Van Den Heuvel et al. J Am Coll Cardiol 1997;30:400-5, Oosterga M et al. Am J Cardiol 2000;87:542-6.

Objectives

- Impact of ACE-Inhibitors on atherosclerotic heart disease
- ACE-Inhibitors and coronary microcirculation
- Anti-ischemic effect of ACE-Inhibitors in patients with risk factors for CAD or documented CAD
- **Future directions - ACE genotyping**

ACE (I/D) genotype as a predictor of the magnitude and duration of the response to IV Enalaprilat in humans



Dose ratios for angiotensin I at 1 hour and 10 hours post dose in II and DD subjects. **P*=0.003 and ***P*=0.001 by Mann-Whitney *U* test. **Circulation 1998;98:2148-2153.**

B-Blockers, ACE-I, and ACE Deletion polymorphism in patients with CHF

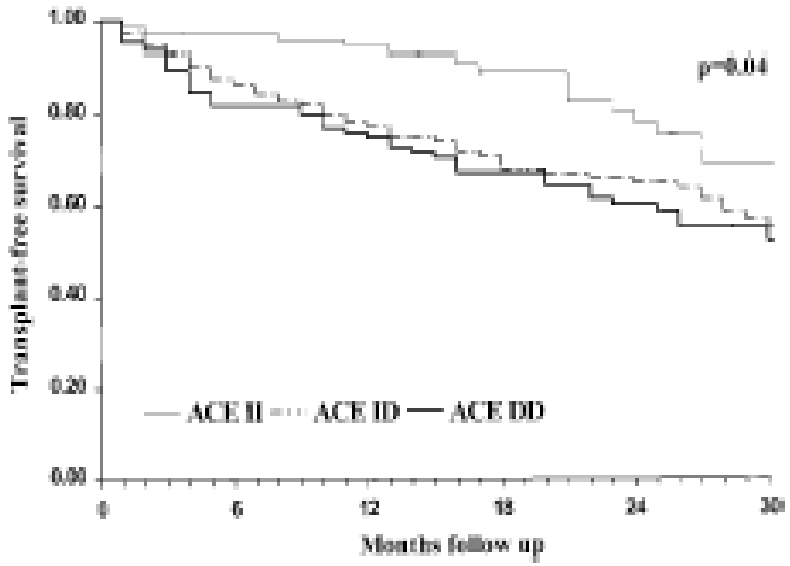


Figure 1. Transplant-free survival compared by *ACE* genotype. Overall cohort, n=328. Ordered log-rank test, *P*=0.044.

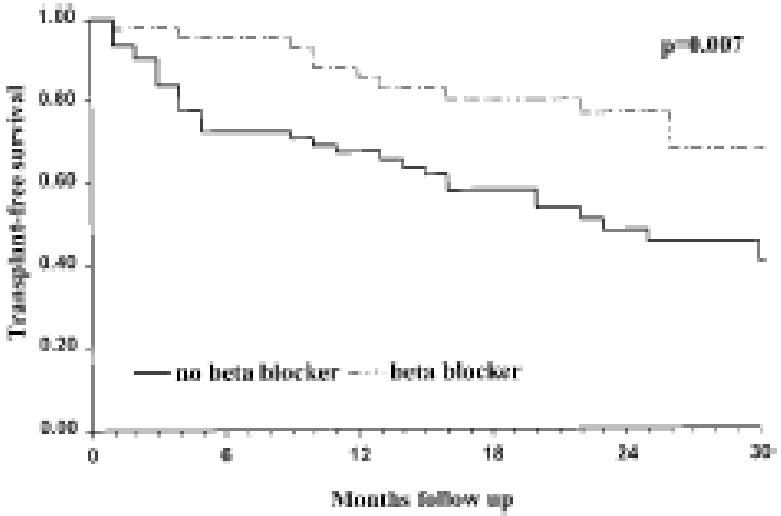


Figure 4. Transplant-free survival compared by β-blocker use for patients with *ACE DD* genotype only, n=105. Event-free survival was significantly better for patients treated with β-blockers (n=43) compared with those not receiving therapy (n=62) (*P*=0.007 by log-rank test).

Transplant free survival is worse in the DD group, however patients in the DD group receiving b-blockers had an almost identical prognosis with those in the II group. **McNamara et al. Circulation 2001;103:1644-48.**

D allele of ACE is a major risk factor for restenosis after coronary stenting

	DD (n=45)	*ID* (n=83)	*II* (n=30)	*P**
MLD at follow-up, mm	1.39±0.12	1.67±0.12	1.90±0.14	<.0001
Diameter stenosis at follow-up, %	49±4	41±4	35±5	<.003
Late loss, mm	1.08±0.12	0.80±0.12	0.57±0.14	<.0001
Net gain, mm	0.71±0.16	0.96±0.15	1.29±0.18	<.0006
Loss index	0.70±0.09	0.50±0.08	0.37±0.10	<.0002

Values are adjusted mean±SEM.
*Adjusted test.

Quantitative Angiography Adjusted for Covariates.

Amant C, et al. Circulation 1997;96:56-60.

Coronary in-stent restenois and ACE polymorphism

- In 369 patients who underwent coronary stenting, the I/D polymorphism of the ACE gene was not a major predictor of in-stent restenosis, however in patients treated versus those not treated with an ACE-I or ARB, there was an increased frequency of ISR in the DD genotypes (40% versus 12%, p=0.006).

Jorgensen E, et al. J Am Coll Cardiol 2001;38:1434-9.

Prescribing Genotyping: Not yet ready, but getting there

- Preliminary data suggest that ACE genotyping may be helpful in patients with heart failure and after coronary interventions given the poorer prognosis of the DD allele
- Identification of other DNA variants (polymorphisms) that may have functional consequences with respect to treatment to b-blockers, ACE-I, ASA etc is the target of the future.
- Further exploration of the renin-aldosterone pathway needed with respect to tissue ACE, dosing in CHF etc.

Circulation 2001;103:1608-10.

BRAZIL 1982 - The team of Dreams

Paolo Roberto Falcao

Socrates

Artunes Coimbra Zico