

**GET HELP FROM
CMS HERE**



Insertion/deletion polymorphism of the angiotensin I-converting enzyme gene is associated with coronary artery plaque calcification as assessed by intravascular ultrasound

M Pfohl, A Athanasiadis, M Koch, P Clemens, N Benda, HU Haring, and KR Karsch
J. Am. Coll. Cardiol. 1998;31:987-991

This information is current as of February 10, 2012

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://content.onlinejacc.org>

JACC

JOURNAL of the AMERICAN COLLEGE of CARDIOLOGY



Insertion/Deletion Polymorphism of the Angiotensin I-Converting Enzyme Gene Is Associated With Coronary Artery Plaque Calcification As Assessed by Intravascular Ultrasound

MARTIN PFOHL, MD, ANASTASIOS ATHANASIADIS, MD, MATTHIAS KOCH, MD, PIA CLEMENS, MD, NORBERT BENDA, PhD, HANS U. HÄRING, MD, KARL R. KARSCH, MD, FACC
Tübingen, Germany

Objectives. We evaluated the influence of the insertion/deletion (I/D) polymorphism of the angiotensin I-converting enzyme (ACE) gene on coronary plaque morphology and calcification in patients with angiographically documented coronary artery disease (CAD).

Background. The ACE I/D polymorphism has been associated with an increased risk of myocardial infarction in patients with the DD genotype but not with the presence of native CAD.

Methods. We studied 146 patients undergoing percutaneous transluminal coronary angioplasty for stable angina pectoris by means of preinterventional intravascular ultrasound (IVUS). Qualitative and quantitative criteria were used to classify the target lesions as poorly or highly echoreflexive or as calcified. Genomic deoxyribonucleic acid was analyzed by polymerase chain reaction (PCR) to identify the I/D polymorphism, with a second insertion-specific PCR in DD genotypes to prevent mistyping.

Results. The ACE genotype groups (DD 46, ID 68, II 32) were well matched for the basic characteristics. Patients with the DD genotype had significantly more calcified lesions (DD 80%, ID 57%, II 66%; unadjusted odds ratio [OR] 2.88, 95% confidence interval [CI] 1.30 to 6.92, $p = 0.008$) and more calcifications $>180^\circ$ of the vessel circumference (DD 22%, ID 10%, II 6%; OR 2.80, 95% CI 1.05 to 7.63, $p = 0.03$). The prevalence of myocardial infarction was not significantly associated with coronary calcification (OR 1.44, 95% CI 0.72 to 2.88, $p = 0.31$).

Conclusions. Patients with CAD and the ACE DD genotype have a significantly higher incidence and greater extent of coronary lesion calcification, as determined by IVUS. This finding indicates that the ACE I/D gene polymorphism is related to the development or progression of atherosclerotic plaque calcification.

(J Am Coll Cardiol 1998;31:987-91)

©1998 by the American College of Cardiology

The insertion/deletion (I/D) polymorphism of the angiotensin I-converting enzyme (ACE) gene has been reported to be associated with myocardial infarction (1,2) and, in some studies, with coronary artery disease (CAD) (3-5). However, these results could not be confirmed in a large prospective trial (6) and in a case-control study (7). A recent study in patients undergoing coronary angiography suggested that the ACE I/D polymorphism is not associated with CAD itself but was closely associated with the occurrence of myocardial infarction (8). Possible reasons for the discrepancies between these studies may be selection bias in some studies (1-4,7,8) and the different genetic backgrounds of the study populations. Another important reason for these discrepancies may be the use of invasive or noninvasive methods for the assessment of CAD (9).

From the Department of Medicine, Division of Endocrinology, Metabolism and Clinical Biochemistry; Division of Cardiology; and Department of Medical Biometry, University of Tübingen, Tübingen, Germany.

Manuscript received August 22, 1997; revised manuscript received December 29, 1997, accepted January 9, 1998.

Address for correspondence: Dr. Martin Pfohl, Eberhard-Karls-Universität Tübingen, Medizinische Klinik und Poliklinik, Abteilung Innere Medizin IV, Offried-Müller-Strasse 10, D-72076 Tübingen, Germany. E-mail: martin.pfohl@t-online.de.

Intravascular ultrasound (IVUS) is a new method for detecting coronary atherosclerosis; its use enables transmural, tomographic imaging of coronary arteries in humans in vivo. This method allows the characterization of coronary plaque composition, including calcium deposits, dense and loose fibrous tissue and intimal hyperplasia (10,11). IVUS is especially useful in detecting the extent of in situ coronary calcium (12). In symptomatic patients with CAD, calcification detected on conventional fluoroscopy has been shown (13) to be associated with an elevated risk of coronary events, and this prognostic relevance of coronary calcification was independent of age and gender.

The purpose of the present study was to use IVUS imaging in human coronary arteries in vivo to analyze the association among plaque morphology, extent of calcification and the ACE I/D genotype in patients with severe CAD.

Methods

Patients. Between October 1994 and February 1996, a series of 146 patients who were scheduled to undergo percutaneous transluminal coronary angioplasty were studied with the use of preinterventional IVUS. Patients were selected from

Abbreviations and Acronyms

ACE	=	angiotensin I-converting enzyme
CAD	=	coronary artery disease
CI	=	confidence interval
D	=	deletion
DNA	=	deoxyribonucleic acid
HDL	=	high density lipoprotein
I	=	insertion
IVUS	=	intravascular ultrasound
LDL	=	low density lipoprotein
OR	=	odds ratio
PCR	=	polymerase chain reaction

a cohort of 826 patients undergoing coronary angioplasty. Selection criteria were stable angina pectoris during adequate medication, absence of severe vessel tortuosity (no bend $>90^\circ$ at the prestenotic, intrastenotic and post-stenotic lesion site) and a reference vessel diameter >2 mm on angiography. The patients had a mean age of 60.0 ± 8.7 years (range 36 to 76); 116 were men, 30 women; and 86 had a history of myocardial infarction. The basic characteristics of the study cohort are provided in Table 1. The study was approved by the local ethics committee, and written informed consent was obtained from each patient before the procedure.

Ultrasound procedures. All patients underwent diagnostic coronary angiography and coronary intervention according to standard techniques. IVUS imaging was performed with a commercially available intracoronary 3.2F monorail catheter operating at 30 MHz (Cardiovascular Imaging Systems, Wiesbaden, Germany), accommodated by the 8F guiding catheter used for coronary angioplasty. Before the coronary angioplasty, the IVUS catheter was advanced through the lesion of interest; after it was positioned distal to this lesion, a slow, manual, continuous pullback was performed. The gain control settings were adjusted to provide an optimal dynamic range. The ultrasound examination was recorded on S-VHS videotape, and the target lesion was analyzed by two independent observers (A.A., K.R.K.) according to qualitative criteria.

Plaque composition was classified as (11–13) *poorly echoreflexive plaque* if $>80\%$ of the plaque area was composed of tissue with an echogenicity less than or equal to that of the adventitia; *highly echoreflexive plaque* if $>80\%$ of the plaque area was composed of tissue producing echoes brighter than that of the adventitia but without acoustic shadowing; and *calcified plaque* if the plaque involved bright echoes with acoustic shadowing $<90^\circ$, 90° to 180° or $>180^\circ$ of the vessel wall circumference.

Laboratory methods. All blood samples were taken after the patients had fasted overnight. Plasma total cholesterol and triglyceride levels were measured by enzymatic methods (Boehringer-Mannheim Biochemica, Mannheim, Germany), and high density lipoprotein (HDL) cholesterol levels were determined after sodium phosphotungstate/magnesium chloride precipitation. Low density lipoprotein (LDL) cholesterol levels were calculated according to the Friedewald formula.

Table 1. Basic Characteristics of 146 Patients by Angiotensin-Converting Enzyme Insertion/Deletion* Genotype

	ACE Genotype		
	DD (n = 46)	ID (n = 68)	II (n = 32)
Male/female	36/10	56/12	24/8
Age (yr)	61.3 ± 9.4	58.0 ± 8.5	62.6 ± 7.4
BMI (kg/m ²)	26.7 ± 2.9	26.9 ± 4.0	26.6 ± 3.2
Never-smoker	15	21	10
Ex-smoker	20	29	16
Current smoker	11	18	6
Hx of MI	58%	60%	56%
Yes/no	27/19	41/27	18/14
Vessel disease			
1	18	37	11
2	17	20	14
3	11	11	7
SBD (mm Hg)	135 ± 21	132 ± 17	138 ± 15
DBP (mm Hg)	80 ± 10	78 ± 11	80 ± 10
Total-C (mg/dl)	190 ± 34	200 ± 38	209 ± 39
LDL-C (mg/dl)	114 ± 30	126 ± 37	124 ± 33
HDL-C (mg/dl)	38 ± 13	40 ± 12	38 ± 10
TGs (mg/dl)			
Median	197	190	212
Range	73–600	64–436	60–589
Vessel examined			
RCA	14	22	9
LAD	30	40	18
LCx	1	5	5
Venous graft	1	1	

*No significant differences between groups, except for age, which is lower for ID than for DD or II ($p < 0.05$). Data presented are mean value \pm SD or number of patients, unless otherwise indicated. ACE = angiotensin-converting enzyme; BMI = body mass index; D = deletion; DBP = diastolic blood pressure; HDL-C = high density lipoprotein cholesterol; Hx = history; I = insertion; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LDL-C = low density lipoprotein cholesterol; MI = myocardial infarction; RCA = right coronary artery; SBP = systolic blood pressure; TGs = triglycerides; Total-C = total cholesterol.

Genomic DNA was isolated and purified from whole blood (from tubes containing EDTA) with the use of QIAamp spin columns according to the manufacturer's instructions (QIAamp Blood Kit, QIAGEN GmbH, Hilden, Germany). ACE genotypes were assessed by PCR using the primer sequences and PCR cycling conditions as described previously (14). The PCR fragments were separated on a horizontal 5% polyacrylamide gel by electrophoresis and visualized by staining with silver solution. All gels were read by two independent observers (M.P., P.C.). According to the absence or presence of the 287-base pair insertion in the PCR product, the patients were classified as homozygous DD, homozygous II or heterozygous ID. To prevent mistyping of ID as DD genotypes, a second PCR with an insertion-specific primer was performed with all samples classified as homozygous DD in the first PCR (14,15). The investigators had no knowledge of the results of the IVUS analysis.

Statistical analysis. Continuous variables are expressed as mean values \pm SD for symmetric distributions and as median

and range for plasma triglyceride levels because of its skewed distribution. The mean values for the three groups (DD, ID and II) were compared by one-way analysis of variance or the Kruskal-Wallis test (plasma triglycerides). Categorical data were assessed using the likelihood ratio test. The analysis was also carried out by means of an explorative multiple logistic regression analysis to assess the independent role of the different factors possibly influencing lesion morphology, with the presence or absence of plaque calcification as dependent variable. For this analysis, the continuous variables age; body mass index; total plasma cholesterol level, HDL and LDL cholesterol levels; and triglyceride levels were each grouped in quartiles. In addition, for the ACE genotype, odds ratios were calculated as a measure of the association with the plaque calcification, with the effects of the D allele assumed to be *additive* (with scores of 0, 1 and 2 for the II, ID and DD genotypes, respectively), *dominant* (with scores of 0 for the II genotypes and 1 for the ID and DD genotypes) or *recessive* (with scores of 0 for the II and ID genotypes and 1 for the DD genotypes). For each odds ratio, the 95% confidence intervals and two-tailed p values were calculated. All analyses were done with use of a personal computer with JMP 3.2 (SAS Institute). A p value <0.05 was considered statistically significant.

Results

The frequencies of the ACE genotypes (DD 46 [31.5%], ID 68 [46.6%] and II 32 [21.9%]) and the D allele (54%) in the 146 patients investigated were virtually identical to those obtained in studies in Europe (1,7) and North America (6), and the distribution was consistent with the study population being in Hardy-Weinberg equilibrium. Thus, with respect to the ACE gene locus, our sample is representative of white populations. The genotype groups were well matched for gender, body mass index and smoker status. Age was significantly lower in the ID group than in the DD and II groups (p = 0.02). Systolic and diastolic blood pressures did not differ among the groups, and there were no significant differences in plasma lipid and lipoprotein levels. The distribution of vessels examined did not differ among the genotype groups (Table 1), and there was no association between the ACE I/D genotype and a history of myocardial infarction (odds ratio [OR] adjusted for age [DD vs. ID + II] 1.05, 95% confidence interval [CI] 0.51 to 2.19, p = 0.89).

Among the DD genotypes, we found significantly fewer noncalcified lesions (Table 2). Eighty percent of patients with the DD genotype had calcified lesions. In contrast, only 57% of patients with ID genotype and 66% of patients with the II genotype had calcified lesions (OR for DD vs. ID + II 2.88, 95% CI 1.30 to 6.92, p = 0.008). Among patients with calcified lesions, those with the DD genotype also had significantly more severe calcifications, with shadowing of >180° of the lumen circumference in 22% of the lesions compared with 10% of those with the ID genotype and 6% of those with the II genotype (OR for DD vs. ID + II 2.80, 95% CI 1.05 to 7.63, p = 0.03). Thus, the DD genotype was associated not only with

Table 2. Intravascular Ultrasound Lesion Characteristics by Angiotensin-Converting Enzyme Genotype

Echorefectivity of Plaque	ACE Genotype		
	DD (n = 46)	ID (n = 68)	II (n = 32)
Noncalcified lesions	9 (20%)	29 (43%)	13 (34%)
Poorly echorefective	9 (20%)	25 (37%)	9 (28%)
Highly echorefective	0 (0%)	4 (6%)	4 (6%)
Calcified lesions	37 (80%)	39 (57%)	21 (66%)
Calcification <90°	16 (34%)	14 (21%)	8 (25%)
Calcification 90° to 180°	11 (24%)	18 (26%)	11 (34%)
Calcification >180°	10 (22%)	7 (10%)	2 (6%)

Data presented are number (%) of patients. Odds ratio 2.88 (95% confidence interval [CI] 1.30 to 6.92, p = 0.008) for calcified versus noncalcified lesions (DD vs. ID + II); odds ratio 2.80 (95% CI 1.05 to 7.63, p = 0.03) for lesions with calcification >180° of target circumference versus lesions with less or no calcification (DD vs. ID + II). Abbreviations as in Table 1.

the presence but also with the extent of coronary plaque calcification. However, coronary plaque calcification, was not significantly associated with a history of myocardial infarction (OR for calcified vs. noncalcified lesions 1.44, 95% CI 0.72 to 2.88, p = 0.31; OR adjusted for age 1.69, 95% CI 0.82 to 3.53, p = 0.16).

Because age and gender have been shown (16) to be the most important risk factors for coronary calcification detected by ultrafast computed tomography in asymptomatic men and women, multiple logistic regression analysis was performed to correct for these and other possible influencing factors. Age was found to be the strongest predictor of coronary plaque calcification (OR 6.03, 95% CI 1.87 to 21.47, p = 0.003), whereas gender, hypertension and a history of smoking were not found to be predictive of plaque calcification (Table 3). In

Table 3. Odds Ratios for Intravascular Ultrasound Coronary Plaque Calcification by ACE Genotype and Other Variables: Multiple Logistic Regression Analysis*

Factor	Chi-Square	OR (95% CI)	p Value
Age	9.29	6.03 (1.87-21.47)	0.0023
ACE DD genotype	7.93	3.69 (1.47-10.19)	0.0049
Male gender	0.93	1.70 (0.58-5.08)	0.34
Hx of MI	2.90	2.08 (0.90-4.98)	0.09
Hx of smoking	1.48	0.56 (0.21-1.42)	0.22
BMI	3.91	0.34 (0.11-0.99)	0.048
Diabetes	0.90	1.63 (0.60-4.71)	0.34
Hypertension†	0.03	0.92 (0.38-2.27)	0.86
Total-C	1.34	3.47 (0.43-30.68)	0.25
HDL-C	1.63	2.29 (0.64-8.61)	0.20
LDL-C	2.13	0.24 (0.03-1.63)	0.14
TGs	4.04	3.91 (1.04-15.79)	0.05

*Age, body mass index (BMI), total cholesterol (Total-C), high density lipoprotein (HDL-C) and low density lipoprotein (LDL-C) cholesterol and triglycerides (TGs) were grouped in quartiles. †Systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or both, at repeated measurements or the current use of antihypertensive agents for a confirmed diagnosis of arterial hypertension. CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

addition to age, the ACE DD genotype again proved to be associated with coronary plaque calcification (OR 3.69, 95% CI 1.47 to 10.19, $p = 0.0049$). There were also no significant relations between coronary plaque calcification and a history of myocardial infarction or plasma lipid and lipoprotein levels (Table 3).

The analysis of the odds ratios between the presence or absence of coronary plaque calcification and the three ACE genotypes, adjusted for age, revealed a recessive effect of the D allele with an adjusted OR of 2.62 in the model comparing the DD genotypes with the ID and II genotypes (95% CI 1.16 to 6.42, $p = 0.02$). Using the model for an additive effect of the D allele, the adjusted odds ratio for the DD versus the ID genotype was 2.72 (95% CI 1.15 to 6.92, $p = 0.02$); for the ID genotype versus the II genotype, the adjusted odds ratio was 0.88 (95% CI 0.35 to 2.18, $p = 0.79$). In the model for the dominant effect of the D allele, the adjusted odds ratio was 1.28 (95% CI 0.53 to 3.00, $p = 0.58$) for the DD and ID genotypes versus the II genotype.

Discussion

The results of the present study showed that the ACE DD genotype is associated with the incidence and extent of coronary calcification as assessed by IVUS. Although the major determinant of coronary plaque calcification is age, the association with the ACE DD genotype persists after correction for age and is stronger than the nonsignificant association between history of myocardial infarction and coronary plaque calcification.

IVUS and plaque calcification. The ability of IVUS to characterize coronary plaque composition and calcification is well documented (10–12). IVUS has been shown (17) to be highly sensitive and specific in detecting dense, coherent calcification in human coronary arteries compared with histologic examination and to be far more sensitive than angiography in the diagnosis of coronary calcification (12). The improved characterization of coronary plaque morphology by IVUS examination led to the finding of an association of plaque calcification with the ACE gene D polymorphism, which was not detected by coronary angiography. This observation could explain why the ACE gene polymorphism seemed not to be associated with native CAD as determined by coronary angiography, but with myocardial infarction in some studies (2,8).

Plaque calcification and coronary events. One of the important findings of this study is the relatively low prevalence of noncalcified lesions. This result is compatible with those in a subgroup of patients with stable angina pectoris in a study (18) using IVUS to identify unstable coronary lesions. However, the inclusion of only patients with stable angina may be a selection bias in the cohort investigated. Although patients with severe coronary plaque calcification may be less prone to acute coronary events than are patients with unstable lesions, the frequency of stable lesions in patients who died abruptly of myocardial infarction has been shown (19) to be ~50%. In

addition, the interface between a calcified region of coronary plaque and the adjacent noncalcified region seems to be exposed to increased mechanical shear stress, resulting in plaque disruption (20). In agreement with these results, and in concordance with the currently accepted theory of plaque rupture, 59% of our patients had a history of myocardial infarction. The increased frequency of calcified lesions among patients with the ACE DD genotype could explain the recently described observation that the beneficial effects of lipid-lowering therapy on ischemic events and angiographically defined coronary stenosis are blunted among patients with the ACE DD genotype (21).

ACE polymorphism and plaque calcification. The significant association of the ACE D polymorphism with coronary plaque calcification is in accordance with the recent findings of Rasmussen and Cedet (22), who described an increased extent of macroscopically visible aortic atherosclerosis at autopsy in both insulin-dependent and -independent diabetic patients who were homozygous or heterozygous for the ACE D allele. In that postmortem study, the ACE gene polymorphism was not related to total collagen and type IV or V collagen, indicating a possible involvement of the ACE gene polymorphism in the later stages of atherosclerosis.

In the past, coronary calcification has been regarded as a passive process of adsorption or precipitation of calcium phosphate crystals. Recently, coronary plaque calcification has been recognized as an organized, regulated process (23). Coronary calcification is absent in the normal arterial vessel wall and seems to occur only late in the development in atherosclerotic lesions (24). The influence of genetic factors on the occurrence of arterial calcification has recently been shown in genetically distinct inbred mice (25). Although the molecular basis for the incorporation of calcium and the extent of this calcification is not completely understood, several proteins involved in bone formation and calcification have been identified in atherosclerotic human coronary artery specimens (26). One of these proteins, osteopontin, a phosphorylated glycoprotein, has been shown (26) to be present at the calcification front of atherosclerotic segments, and osteopontin mRNA expression by macrophages has been demonstrated to be related to the severity of atherosclerosis (27). In addition to basic fibroblast growth factor and transforming growth factor- β , angiotensin II is known to increase the osteopontin mRNA and protein expression in vascular smooth muscle cells *in vitro* (28). Both circulating (29) and local (30) cardiac activities of ACE are higher in the presence of the ACE gene D polymorphism, which might increase the conversion of the inactive angiotensin I to the highly active angiotensin II. Thus, it can be speculated that in addition to its documented role in vasoconstriction and vascular smooth muscle cell growth (31), the renin-angiotensin system may also be involved in the regulation of calcification in atherosclerotic arteries.

Study limitations. This study is limited by the possible selection bias due to the inclusion of only patients with stable angina and to the relatively low number of patients. The number of patients examined was too low to find or exclude

associations between ACE I/D gene polymorphism and myocardial infarction, so the relation among ACE polymorphism, coronary plaque calcification and myocardial infarction remains somewhat speculative. In addition, the lack of association among the plasma lipids, hypertension and diabetes on the coronary plaque morphology must be interpreted with caution because the duration and modification of these risk factors were not known. Furthermore, the mechanisms by which the intronic ACE I/D polymorphism could influence coronary plaque calcification are hypothetical. Probably, the ACE I/D polymorphism is only a marker for the functional polymorphism or mutation that influences coronary plaque calcification, so the linkage disequilibrium between the two polymorphisms may be limited to the cohort examined. However, an association between the ACE I/D gene polymorphism and the carotid artery wall thickness has recently been reported (32) in an ethnically distinct group of Japanese patients with non-insulin-dependent diabetes mellitus, indicating an involvement of this ACE polymorphism in the development or progression of atherosclerosis in different populations and vessel regions.

Conclusions. The findings of the present study suggest that in addition to age, the ACE DD genotype is an independent determinant of the incidence and extent of coronary plaque calcification in patients with stable angina pectoris. This observation is a possible explanation for the increased risk of cardiovascular events in patients with CAD who have the ACE DD genotype.

References

- Cambien F, Poirier O, Lecerf L, et al. Deletion polymorphism in the gene for angiotensin-converting enzyme is a potent risk factor for myocardial infarction. *Nature* 1992;359:641-4.
- Wang XL, McCredie RM, Wilcken DEL. Genotype distribution of angiotensin-converting enzyme polymorphism in Australian healthy and coronary populations and relevance to myocardial infarction and coronary artery disease. *Arterioscler Thromb Vasc Biol* 1996;16:115-9.
- Nakai K, Itoh C, Miura Y, et al. Deletion polymorphism of the angiotensin I-converting enzyme gene is associated with serum ACE concentration and increased risk for CAD in the Japanese. *Circulation* 1994;90:2199-202.
- Ruiz J, Blanche H, Cohen N, et al. Insertion/deletion polymorphism of the angiotensin-converting enzyme gene is strongly associated with coronary heart disease in non-insulin-dependent diabetes mellitus. *Proc Natl Acad Sci USA* 1994;91:3662-5.
- Mattu RK, Needham EW, Galton DJ, Frangos E, Clark AJ, Caulfield M. A DNA variant at the angiotensin-converting enzyme gene locus associates with coronary artery disease in the Caerphilly Heart Study. *Circulation* 1995;91:270-4.
- Lindpaintner K, Pfeffer MA, Kreutz R, et al. A prospective evaluation of an angiotensin-converting-enzyme gene polymorphism and the risk of ischemic heart disease. *N Engl J Med* 1995;332:706-11.
- Friedl W, Krempler F, Paulweber B, Pichler M, Sandhofer F. A deletion polymorphism in the angiotensin converting enzyme gene is not associated with coronary heart disease in an Austrian population. *Atherosclerosis* 1995;112:137-43.
- Ludwig E, Corneli PS, Anderson JL, Marshall HW, Lalouel JM, Ward RH. Angiotensin-converting enzyme gene polymorphism is associated with myocardial infarction but not with development of coronary stenosis. *Circulation* 1995;91:2120-4.
- Singer DRJ, Missouri CG, Jeffery S. Angiotensin-converting enzyme polymorphism: what to do about all the confusion? *Circulation* 1996;94:236-9.
- Mintz GS, Popma JJ, Pichard AD, et al. Limitations of angiography in the assessment of plaque distribution in coronary artery disease: a systematic study of target lesion eccentricity in 1446 lesions. *Circulation* 1996;93:924-31.
- Kimura BJ, Bhargava V, DeMaria AN. Value and limitations of intravascular ultrasound imaging in characterizing coronary atherosclerotic plaque. *Am Heart J* 1995;130:386-96.
- Mintz GS, Popma JJ, Pichard AD, et al. Patterns of calcification in coronary artery disease: a statistical analysis of intravascular ultrasound and coronary angiography in 1155 lesions. *Circulation* 1995;91:1959-65.
- Detrano R, Hsias T, Wang S, et al. Prognostic value of coronary calcification and angiographic stenoses in patients undergoing coronary arteriography. *J Am Coll Cardiol* 1996;27:285-90.
- Koch M, Lehmann R, Pfohl M, Voelter W, Liebich H. Analysis of the deletion/insertion polymorphism of the angiotensin I-converting enzyme gene by capillary electrophoresis. *Clin Chim Acta* 1996;248:197-203.
- Shanmugan V, Sell KW, Saha K. Mistyping ACE heterozygotes. *PCR Methods Appl* 1993;3:120-1.
- Goel M, Wong ND, Eisenberg H, Hagar J, Kelly K, Tobis JM. Risk factor correlates of coronary calcium as evaluated by ultrafast computed tomography. *Am J Cardiol* 1992;70:977-90.
- Friedrich GJ, Moes NY, Muhlberger VA, et al. Detection of intralumenal calcium by intracoronary ultrasound depends on the histologic pattern. *Am Heart J* 1994;128:435-41.
- Hodgson JM, Reddy KG, Suneja R, Nair RN, Lesnefsky EJ, Sheehan HM. Intracoronary ultrasound imaging: correlation of plaque morphology with angiography, clinical syndrome and procedural results in patients undergoing coronary angioplasty. *J Am Coll Cardiol* 1993;21:35-44.
- Farb A, Tang AL, Burke AP, Sessums L, Liang Y, Virmani R. Sudden coronary death: frequency of active coronary lesions, inactive coronary lesions, and myocardial infarction. *Circulation* 1995;92:1701-9.
- Falk E, Shah PK, Fuster V. Coronary plaque disruption. *Circulation* 1995;92:657-71.
- Rasmussen LM, Ledet T. Aortic atherosclerosis in diabetes mellitus is associated with an insertion/deletion polymorphism in the angiotensin I-converting enzyme gene. *Diabetologia* 1996;39:696-700.
- Van Geel PP, Pinto YM, Zwinderman AH, et al. The angiotensin-converting enzyme deletion-type gene is associated with ischemic events and a blunted effect of lipid-lowering treatment on angiographically defined coronary atherosclerosis [abstract]. *Eur Heart J* 1997;18 Suppl:141.
- Wrexler L, Brundage B, Crouse J, et al. Coronary artery calcification: pathophysiology, epidemiology, imaging methods, and clinical implications. *Circulation* 1996;94:1175-92.
- Simons DB, Schwartz RS, Edwards WD, Sheedy PF, Breen JF, Rumberger JA. Noninvasive definition of anatomic coronary artery disease by ultrafast computed tomographic scanning: a quantitative pathologic comparison study. *J Am Coll Cardiol* 1992;20:1118-26.
- Qiao JH, Xie PZ, Fishbein MC, et al. Pathology of atheromatous lesions in inbred and genetically engineered mice: genetic determination of arterial calcification. *Arterioscler Thromb* 1994;14:1480-97.
- Fitzpatrick LA, Severson A, Edwards WD, Ingram RT. Diffuse calcification in human coronary arteries: association of osteopontin with atherosclerosis. *J Clin Invest* 1994;94:1597-604.
- Hirota S, Imakita M, Kohri K, et al. Expression of osteopontin messenger RNA by macrophages in atherosclerotic plaques: a possible association with calcification. *Am J Pathol* 1993;143:1003-8.
- Giachelli CM, Bae N, Almeida M, Denhardt DT, Alpers CE, Schwartz SM. Osteopontin is elevated during neointima formation in rat arteries and is a novel component of human atherosclerotic plaques. *J Clin Invest* 1993;92:1686-96.
- Rigat B, Hubert C, Alhenc-Gelas F, Cambien F, Corvol P, Soubrier F. An insertion/deletion polymorphism in angiotensin I converting enzyme gene accounting for half of the variance of serum enzyme levels. *J Clin Invest* 1990;86:1343-6.
- Danser JAH, Schalekamp MADH, Bax WA, et al. ACE in the human heart: effect of the deletion/insertion polymorphism. *Circulation* 1995;92:1387-8.
- Daemen MJAP, Lombardi DM, Bosman FT, Schwartz SM. Angiotensin II induces smooth muscle cell proliferation in the normal and injured rat arterial wall. *Circ Res* 1991;68:450-68.
- Hosoi M, Nishizawa Y, Kogawa K, et al. Angiotensin-converting enzyme gene polymorphism is associated with carotid arterial wall thickness in non-insulin-dependent diabetic patients. *Circulation* 1996;94:704-7.

Insertion/deletion polymorphism of the angiotensin I-converting enzyme gene is associated with coronary artery plaque calcification as assessed by intravascular ultrasound

M Pfohl, A Athanasiadis, M Koch, P Clemens, N Benda, HU Haring, and KR Karsch
J. Am. Coll. Cardiol. 1998;31;987-991

This information is current as of February 10, 2012

Citations	This article has been cited by 11 HighWire-hosted articles: http://content.onlinejacc.org#otherarticles
Rights & Permissions	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://content.onlinejacc.org/misc/permissions.dtl
Reprints	Information about ordering reprints can be found online: http://content.onlinejacc.org/misc/reprints.dtl