

## Effect of Risk Factors on the Mechanism of Acute Thrombosis and Sudden Coronary Death in Women

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**Background**—Traditional risk factors have been linked to atherosclerotic heart disease in women. However, the effect of risk factors and menopausal status on the mechanism of sudden coronary death is unknown.

**Methods and Results**—We examined 51 cases of sudden coronary death and 15 hearts from women who died of trauma. Coronary deaths were divided into four mechanisms of death: ruptured plaque with acute thrombus (n=8), eroded plaque with acute thrombus (n=18), stable plaque with healed infarct (n=18), and stable plaque without infarction (n=7). Vulnerable plaques prone to rupture were defined as those with a thin, fibrous cap infiltrated by macrophages and were quantitated in coronary deaths and control subjects. Total cholesterol (TC), HDL cholesterol, glycosylated hemoglobin, cigarette smoking, and hypertension were determined in each case. Compared with control subjects, women with plaque ruptures had elevated TC ( $270 \pm 55$  versus  $194 \pm 44$  mg/dL,  $P=0.002$ ), and those with erosions were more likely to be smokers (78% versus 33%,  $P=0.01$ ). Women with stable plaque and healed infarct had elevated glycosylated hemoglobin ( $10.2 \pm 5.0\%$  versus  $6.4 \pm 0.4\%$  in control subjects,  $P=0.001$ ) and were more likely to be hypertensive (50% versus 15% in control subjects,  $P=0.03$ ). By multivariate analysis, cigarette smoking was associated with plaque erosion ( $P=0.03$ , odds ratio [OR] 21), glycosylated hemoglobin with stable plaque and healed infarct ( $P=0.03$ , OR 41), TC with plaque rupture ( $P=0.02$ , OR 7), and hypertension with stable plaque with healed infarct ( $P=0.02$ , OR 15). Seven of 8 plaque ruptures occurred in women  $>50$  years of age versus 3 of 18 erosions ( $P=0.001$ ). In cases of coronary death, vulnerable plaques were associated with elevated cholesterol ( $P=0.002$ ) and age  $>50$  years ( $P=0.002$ ), independent of other risk factors.

**Conclusions**—In women, traditional risk factors have distinct effects on the mechanisms of sudden coronary death, which vary by menopausal status. Effective risk factor modification may therefore differ between younger and older women and may be targeting different mechanisms of plaque instability. (*Circulation*. 1998;97:2110-2116.)

**Key Words:** thrombosis ■ death, sudden ■ risk factors ■ women

Sudden cardiac death occurs in 300 000 people in the United States annually,  $>80\%$  of which are due to coronary causes.<sup>1</sup> Because it has been estimated that up to 50% of coronary deaths are sudden,<sup>1,2</sup> pathologic observations about sudden coronary death are likely to reflect a fairly large proportion of patients who suffer from atherosclerotic coronary disease.

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Although the incidence of sudden death is approximately four times greater in men than women,<sup>3</sup> this difference decreases with advancing age.<sup>4</sup> Estrogen has been implicated as a protective mechanism against the development of atherosclerosis. The effect of estrogen on the inhibition of atherosclerosis is poorly understood but may be related to lipoprotein metabolism<sup>5</sup> or its effect on vascular smooth

muscle.<sup>5,6</sup> The protective effect of estrogen against atherosclerotic vascular disease is one of the major reasons to prescribe estrogen replacement treatment in postmenopausal women.<sup>7</sup>

Coronary risk factors have been well established in men and include cigarette smoking, dyslipidemia, diabetes mellitus, and hypertension.<sup>3</sup> In women, hyperlipidemia (elevated total cholesterol [TC], low HDL-C, and hypertriglyceridemia), cigarette smoking, and diabetes mellitus have been linked to coronary artery disease, sudden death, and myocardial infarction.<sup>2,8-13</sup> We have recently shown that in men, cigarette smoking is associated with coronary thrombosis and dyslipidemia with plaque rupture.<sup>14</sup> It is unknown whether similar associations exist for women, especially given the likely effects of estrogen on the morphology of atherosclerosis.

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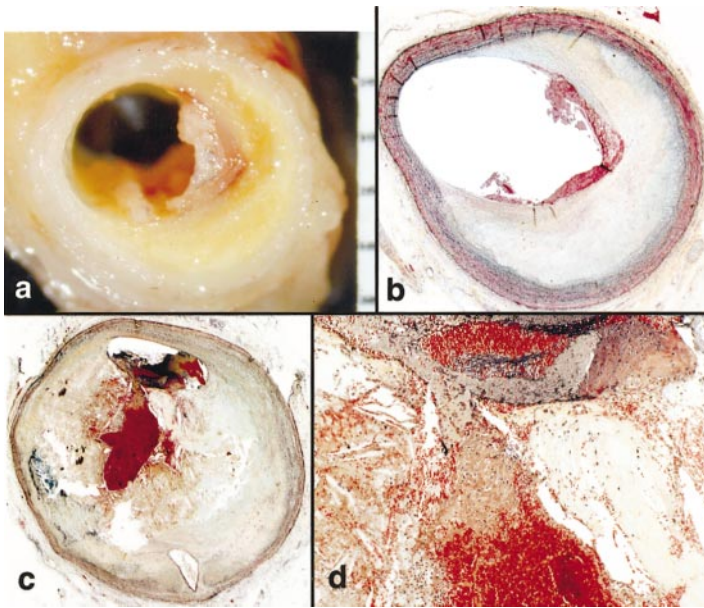
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Substrates of acute coronary thrombosis. a, Plaque erosion: eccentric plaque with overlying subocclusive thrombus. The narrowing is not critical, and disruption of the cap is absent. b, Microscopic illustration of a demonstrates thrombus overlying intact plaque. The patient was a 58-year-old smoker with a history of emphysema but no heart disease. She recently complained of chest pain but was not extensively evaluated. She had an apparent seizure and developed cardiac arrest from which she could not be resuscitated. c, Plaque rupture: Critical narrowing of this section of left anterior descending artery by atheroma rich in cholesterol crystals. Central hemorrhage into plaque is continuous with the small residual lumen above. Black reflects the postmortem injection of contrast material. d, Higher magnification of c demonstrates rupture site.

The purpose of this study was to determine whether risk factors affect the mechanism of coronary death in women (specifically the plaque morphology underlying thrombosis and incidence of healed infarcts) and whether these mechanisms are modified by age >50 years or <50 years (a likely reflection of menopausal status). The results of this study should aid in targeting coronary risk factor modification and therapy in women with coronary artery disease.

## Methods

### Case Selection

Female victims of sudden death were identified at the Office of the Chief Medical Examiner of the State of Maryland. When an autopsy was performed, the heart was examined in consultation with the Department of Cardiovascular Pathology at the Armed Forces Institute of Pathology. These cases were evaluated prospectively in a similar manner during the same time period as previously reported in men.<sup>14</sup> Fifteen control subjects who died of trauma were collected during the same study period. The trauma cases were chosen only if the age of the victim fell within the approximate study range (that is, >35 years of age). Risk factors (with the exception of age) were not known before inclusion into the study in any case.

### Heart Study and Determination of Death Category

All hearts were studied under supervision of the medical examiner as previously described.<sup>14</sup> Ten cases were published previously without risk factor data other than hypertension.<sup>15</sup> Briefly, hearts were perfusion fixed in buffered formalin, and epicardial arteries were serially sectioned at 2- to 3-mm intervals. Each segment with >50% cross-sectional area luminal narrowing (estimated at gross examination) was submitted for histology, including Movat pentachrome stains. Coronary deaths were defined as natural deaths without extracardiac cause of death and in which  $\geq 1$  epicardial coronary arteries had >75% cross-sectional area lumen narrowed by atherosclerotic plaque or plaque with superimposed thrombus. Mean cross-sectional luminal area narrowing was determined by computerized morphometry of maximal narrowing of any epicardial artery and plaque underlying acute thrombus (Figure).

Because deaths referred to the medical examiner are unexpected, all coronary deaths were classified as sudden as previously defined.<sup>14,16</sup> Sudden death was defined as symptoms commencing within 6 hours of death (witnessed arrest) or death that occurred within 24 hours of the time that the victim was last seen alive in his

normal state of health. Coronary deaths with acute thrombus were further categorized as plaque rupture if serial sectioning showed a connection between the thrombus and the necrotic core.

Vulnerable plaques were defined as a fibrous cap thinner than 65  $\mu\text{m}$  infiltrated by macrophages overlying a necrotic core as previously defined.<sup>14</sup> In each heart, the mean number of vulnerable plaques was tabulated by counting the number of segments with >50% luminal narrowing with histologic features of vulnerable plaque. In coronary deaths without acute thrombus, the category of death was assigned as stable plaque with healed myocardial infarct and stable plaque without healed infarct.<sup>14</sup>

### Definition of Plaque Erosion

Plaque erosions were defined as an acute thrombus without features of plaque rupture. They consisted of an acute thrombus in direct contact with intimal plaque rich in smooth muscle cells with surrounding proteoglycan matrix. Necrotic core was either absent or poorly defined and when present was not in close proximity to the luminal thrombus.

### Determination of Risk Factors and Menopausal Status

The postmortem serum evaluation of TC, HDL-C, and thiocyanate was performed as previously described.<sup>14,17,18</sup> A thiocyanate level of  $\geq 90$  mg/dL was considered evidence for cigarette smoking.<sup>17,18</sup> The evaluation of glycosylated hemoglobin on red blood cells and the evaluation of hypertension with renal morphometric vascular analysis have also been reported.<sup>14</sup> Cases were discarded if there was gross hemolysis or if evaluation of total protein and serum albumin indicated hemoconcentration or hemodilution. The body mass index was estimated with the formula body weight/body height<sup>2</sup> ( $\text{kg}/\text{m}^2$ ).

Investigators at the scene of death recorded all medications including estrogens, and autopsy and scene investigation resulted in knowledge of previous oophorectomy, if any. Dates of last menstrual periods were not known. An age of 50 years was considered an approximation for onset of menopause. The gross appearance and presence of the uterus and ovaries were evaluated in each case.

### Statistical Analysis

Five categories of sudden death were considered, four coronary and one noncoronary: (1) acute plaque rupture, (2) acute plaque erosion, (3) stable plaque and healed infarct, (4) stable plaque and no healed infarct, and (5) trauma deaths. For univariate analysis, continuous variables (TC, HDL-C, glycosylated hemoglobin, and age) were compared among these five groups by comparisons of means

(ANOVA means table). Categorical variables (smoking status, presumed menopausal status, [age >50 years], hypertension) were compared among these five groups by contingency tables and  $\chi^2$  analysis. For multivariate analysis, logistic regression was performed four times separately to compare the control group with each of the four coronary death groups by using age and risk factors as independent variables (dependent variable=coronary versus control death). TC, HDL-C, and percent glycosylated hemoglobin were treated as continuous variables for determination of *P* values; for determination of odds ratios, a level of 210 mg/dL was used as a normal limit for cholesterol, 45 mg/dL for a normal limit for HDL-C, and 10% as an upper limit for the determination of diabetes mellitus.<sup>14</sup> To test the association between vulnerable plaques and risk factors, only coronary deaths were studied. For univariate analysis, simple regression was used to test for an association between numbers of vulnerable plaques and continuous risk factor data in the four coronary groups. For categorical variables, mean numbers of vulnerable plaques in each heart were compared by Student's *t* test. ANOVA was used to test the association between the independent risk factor variables on the number of vulnerable plaques in each heart. Age >50 years was considered a categorical variable as an indicator of menopausal status.

## Results

### General Clinical and Pathologic Data: Coronary Deaths

For sudden unexpected deaths, a total of 105 cases were initially collected. Seven were eliminated because of incomplete risk factor data based on hemolysis, hemodilution, or inadequate cells for the determination of glycohemoglobin. Of the 98 cases with serologic and blood data, the type of sudden death was determined after full autopsy and serial coronary artery evaluation. Forty-seven cases were excluded on the basis of lack of severe coronary disease (<75% maximal cross-sectional luminal narrowing in the absence of coronary thrombosis), resulting in 51 coronary deaths. In addition, 15 cases of traumatic death were studied in an identical fashion.

Of the 51 coronary deaths, 21 occurred in women >50 years of age and 30 in women  $\leq$ 50 years of age. Acute thrombus overlying plaque erosion was present in 18 hearts (35%), acute thrombus overlying plaque rupture in 8 (16%), stable plaque with healed myocardial infarct in 18 (35%), and stable plaque without infarct in 7 (14%). The mean number of segments studied (those with >50% cross-sectional luminal narrowing) were  $7 \pm 5$  in cases of plaque erosion,  $10 \pm 4$  in cases of plaque rupture,  $12 \pm 8$  in cases of stable plaque with healed infarct, and  $7 \pm 4$  in cases of stable plaque without healed infarct. The number of segments with >50% cross-sectional luminal narrowing was  $12 \pm 11$  in women >50 years of age and  $7 \pm 4$  in women younger than <50 years of age ( $P=0.05$ ). The number of severely narrowed segments (>75% cross-sectional luminal narrowing) was  $2.7 \pm 1.7$  in cases of plaque erosion,  $4.0 \pm 1.1$  in cases of plaque rupture,  $4.2 \pm 1.3$  in cases of stable plaque with healed infarct, and  $3.1 \pm 2.0$  in cases of stable plaque without healed infarct. Severely narrowed segments were significantly fewer in cases of plaque erosion compared with plaque rupture ( $P=0.05$ ) and stable plaque with healed infarct ( $P=0.004$ ). The total number of coronary histologic sections examined was  $28 \pm 13$  in cases of acute plaque rupture,  $25 \pm 14$  in cases of plaque erosion,  $25 \pm 13$  in cases of stable plaque with

healed infarct, and  $14 \pm 5$  in cases of stable plaque without healed infarct.

Thirty-six (71%) of coronary deaths were witnessed (11 of 18 plaque erosions, 7 of 8 plaque ruptures, 11 of 18 stable plaques with healed infarcts, and 7 of 7 stable plaques without healed infarcts). Of the 36 witnessed coronary deaths, 8 (22%) women had chest pain, 12 (33%) complained of symptoms other than chest pain immediately before death, and 16 (45%) did not complain of symptoms. There was no correlation between category of death and presence of chest pain. Symptoms in women who did not complain of chest pain included back pain (2), dizziness (3), nausea and vomiting (1), fever and chills (1), stomach distention (1), left shoulder tingling (1), shortness of breath (1), malaise (1), and fatigue (1). None of the witnessed deaths occurred during exertion. A history of "heart disease" was present in 9 women with sudden coronary death (7 of 18 with stable plaque and healed infarcts, 1 of 8 with plaque rupture, and 1 of 8 with stable plaque without healed infarct), 2 of whom had a documented history of previous myocardial infarction (both with healed infarcts at autopsy). Other medical conditions included known hypertension (11), breast carcinoma (1), carotid endarterectomy (1), depression (3), emphysema (1), known hypercholesterolemia (1), insulin-dependent diabetes mellitus (5), asthma (1), alcoholism (2), glomerulonephritis (1), seizure disorder (1), schizophrenia (1), mitral valve prolapse (1), and lupus erythematosus (1). Fifteen women were receiving oral medications; one was receiving estrogen replacement therapy and 5 were receiving insulin for diabetes mellitus. Oral medications included amitriptyline, aminophylline, atenolol, sertraline, clonidine, furosemide, enalapril, alprazolam, coumadin, dilantin, metoprolol, hydrochlorothiazide, chlorpromazine, amlodipine, methyl dopa, hydrochlorothiazide, sulfazoxazole, ranitidine, prednisone, and diltiazem. The patient receiving estrogen replacement was a 46-year-old woman (status post-hysterectomy/oophorectomy) with an eroded plaque. Other surgeries included mastectomy (1), hysterectomy without oophorectomy (1), and cholecystectomy and tubal ligation (4).

The mean heart weight in hearts with plaque rupture ( $483 \pm 108$  g) and stable plaque with healed myocardial infarct ( $460 \pm 105$ ) exceeded that of hearts with plaque erosion ( $372 \pm 87$  g) ( $P=0.01$ ). The mean heart weight in 7 hearts with stable plaque and no myocardial infarct was  $375 \pm 128$  g.

### General Clinical and Pathologic Data: Noncoronary Deaths

The 15 trauma cases were  $50 \pm 19$  years of age, with a heart weight of  $384 \pm 86$  g. The mean heart weight of trauma deaths was significantly less than that of hearts with plaque rupture ( $P=0.02$ ) and stable plaque with healed infarct ( $P=0.02$ ). The maximum percent coronary stenosis for the trauma deaths was  $13 \pm 16\%$ .

### Risk Factors and Mechanism of Death

In the 66 women, there were no significant differences between TC in women <50 years of age ( $194 \pm 63$  mg/dL) versus women >50 years of age ( $221 \pm 61$  mg/dL,  $P=0.11$ ). HDL cholesterol was similar in both groups ( $47 \pm 18$  versus

**TABLE 1. Risk Factors and Mechanism of Death: 51 Women With Severe Coronary Atherosclerosis**

Risk Factor	Plaque Rupture (n=8)	Plaque Erosion (n=18)	Stable Plaque, Healed MI (n=18)	Stable Plaque, no MI (n=7)	P Values (if <0.05)
Age, y, mean±SD	58±12*	45±8†	54±13	43±9	*0.01 vs erosion; 0.02 vs stable, no MI;† 0.04 vs stable plaque, healed MI
Age >50 y, n (%)	7 (87%)*	3 (17%)	9 (50%)	2 (29%)	*0.001 vs plaque erosion; 0.03 vs stable plaque, no infarct
TC, mg/dL, mean±SD	270±55*	188±48	203±71	201±57	*0.007 vs erosion; 0.007 vs stable plaque, healed MI; 0.02 vs stable plaque
HDL-C, mg/dL, mean±SD	46±12	39±21	40±23	48±32	...
TC/HDL-C, mean±SD	6.2±1.8	6.0±3.7	6.6±3.9	5.2±2.7	...
BMI, kg/m <sup>2</sup> , mean±SD	31±4*	27±4	28±9	30±11	*0.02 vs erosion
GlycoHgb, %, mean±SD	8.8±4.4	6.7±0.7	10.2±5.0*	8.0±4.5	*0.006 vs erosion
Ht wt, g, mean±SD	483±108	372±87*	460±105	375±129	*0.01 vs rupture and stable plaque, healed MI
Ht wt/BMI, mean±SD	1.6±0.5	1.4±0.4	1.7±0.4*	1.3±0.2	*0.02 vs stable plaque; 0.04 vs erosion
Smokers, n (%)	4 (50%)	14 (78%)	9 (50%)	2 (29%)	...
Htn, n (%)	3 (38%)	4 (22%)	9 (50%)	2 (29%)	...

MI indicates myocardial infarct; TC, total cholesterol; HDL-C, HDL, cholesterol; Ht wt, heart weight; BMI, body mass index; GlycoHgb, glycosylated hemoglobin; and Htn, hypertension.

\*Statistically significant differences between values within the same row.

†Statistically significant differences between values within the same row.

42±24 mg/dL, respectively,  $P=0.4$ ), as was the frequency of presumed cigarette smoking (50% versus 58%, respectively). Percent glycohemoglobin was lower in young women ( $7.1\pm2.4\%$  versus  $9.3\pm5.6\%$ , respectively,  $P=0.04$ ), as was the frequency of hypertension (20% versus 48%,  $P=0.03$ ). Body mass index was similar in young and older women ( $29\pm8.3$  kg/m<sup>2</sup> versus  $28\pm7$  kg/m<sup>2</sup>, respectively,  $P=0.4$ ). The mean heart weight was greater in women >50 years of age ( $454\pm124$  g) than in women  $\geq 50$  years of age ( $385\pm84$  g,  $P=0.009$ ).

For each of the four categories of coronary deaths, mean age, TC, HDL-C, body mass index, and percent glycosylated hemoglobin are presented in Table 1. Women with plaque rupture were significantly older than women with eroded plaque and stable plaque without myocardial infarct, and women with plaque erosion were significantly younger than

those with stable plaque and healed infarct. The TC levels of women with plaque rupture were significantly elevated compared with women with stable plaque and women with plaque erosion. HDL-C and TC/HDL did not significantly differ among the groups. Body mass index was significantly greater in plaque rupture compared with plaque erosion. Percent glycohemoglobin was significantly higher in stable plaque with healed infarct compared with eroded plaque. Heart weight was less in hearts with acute erosion compared with hearts with stable plaque and healed infarct and hearts with acute rupture. When taken in relation to body mass index, the heart weight was greatest in women with stable plaque and healed infarct.

Compared with control subjects, women with acute ruptures had higher total cholesterol levels and higher heart weights (Table 2). TC/HDL-C was significantly higher in

**TABLE 2. Risk Factors: 15 Control Subjects, Comparison With Coronary Deaths by Mechanism (Univariate Analysis)**

Risk Factors	Trauma Control Subjects (n=15)	P vs Acute Ruptures (n=8)	P vs Acute Erosions	P vs Stable Plaque, Healed MI
TC, mg/dL, mean±SD	194±44	<b>0.002</b>	0.17	0.6
Smokers, n (%)	5 (33%)	0.4	<b>0.01</b>	0.3
GlycoHgb, %, mean±SD	6.4±0.4	0.1	0.8	<b>0.001</b>
Htn, n (%)	2 (15%)	0.2	0.2	<b>0.03</b>
TC/HDL-C, mean±SD	4.3±1.7	<b>0.03</b>	0.2	<b>0.05</b>
Ht wt, g, mean±SD	384±86	<b>0.03</b>	0.7	<b>0.03</b>
Ht wt/BMI, mean±SD (m <sup>2</sup> ×10)	1.3±0.3	0.1	0.4	<b>0.006</b>
BMI, kg/m <sup>2</sup> , mean±SD	31±9	0.9	0.14	0.8
Age, y, mean±SD	50±16	0.3	0.2	0.5
HDL-C, mg/dL, mean±SD	50±19	0.6	0.2	0.2

See Table 1 abbreviations. Bold numbers indicate statistically significant differences,  $P<0.05$ .

**TABLE 3. Risk Factors in Women Who Died of Severe Coronary Disease: Multivariate Comparison With Control Subjects by Mechanism of Death**

Mechanism of Death	Risk Factor	<i>P</i> vs Control Subjects	Odds Ratio vs Control Subjects
Plaque rupture	Total cholesterol	0.02	7†
	Low HDL-C	0.14	
	Age	0.2	
	Others	>0.4	
Plaque erosion	Smoking	0.03	21
	Hypertension	0.2	
	Low HDL-C	0.19	
	Age*	0.17	
	Total cholesterol*	0.2	
	Others	>0.4	
Stable plaque, healed MI	Hypertension	0.02	15
	GlycoHgb	0.03	41‡
	Total cholesterol	0.17	
	Heart weight	0.2	
	Smoking	0.3	
	Others	>0.4	

See Table 1 abbreviations.

Multivariate analysis using stepwise logistic regression, *P*=0.4 for removing, *P*=0.2 for entering. Odds ratios given only if *P*<0.05.

\*Negative association.

†Odds ratio calculated if used as dichotomous variable, cutoff 210 mg/dL for TC, 10%. Odds ratio as continuous variable, 1.04.

‡Odds ratio calculated if used as dichotomous variable, cutoff 10% glycosylated hemoglobin. Odds ratio as continuous variable, 9.

women with stable plaque and healed infarct than in control subjects. Women with plaque erosion were more likely to be smokers than were control subjects (Table 2). Women with stable plaque and healed infarct were more likely to be hypertensive and had elevated glycosylated hemoglobin (Table 2). By multivariate analysis, these associations were independent of other risk factors (Table 3). Compared with control subjects, the odds ratio of elevated TC >210 mg/dL was 7 in women with plaque rupture, and the odds ratio of smoking in women with erosion was 21 compared with control subjects. The odds ratio of hypertension was 15, and the odds ratio of elevated glycosylated hemoglobin >10% was 41 in women with stable plaque and healed myocardial infarct versus control subjects. There were no significant associations between risk factors and stable plaque without healed infarct.

### Incidence of Infarcts and Degree of Coronary Narrowing: Coronary Deaths

Acute myocardial infarcts were present in 8 of 18 plaque erosions, 2 of 8 plaque ruptures, 2 of 18 stable plaques with healed infarcts, and none of 7 stable plaques without healed infarcts. The maximal percent coronary artery stenosis in any artery (not necessarily that with thrombus) was 88±10% for stable plaque with healed infarct, 81±11% for plaque rupture, 81±6% for stable plaque without healed infarct, and

**TABLE 4. Mean Vulnerable Plaques in Hearts From 51 Women Who Died Suddenly With Severe Coronary Disease, Compared by Presence of Risk Factors**

Risk Factor	Mean Vulnerable Plaques, n±SD, Quantitated in Each Heart	<i>P</i> Value
Age ≤50 y	0.2±0.4	<0.0001
Age >50 y	1.3±0.9	
Normal cholesterol	0.3±0.5	0.03
TC >210+TC/HDL:C >5	1.1±1.1	
Normal glycohemoglobin	0.6±0.7	0.2
Glycohemoglobin >10	1.0±1.2	
Nonsmoker	0.4±0.8	0.09
Smoker	0.8±0.1	
Normal weight	0.5±0.9	>0.5
BMI >28	0.8±0.9	
Normotensive	0.4±0.8	>0.5
Hypertensive	0.6±0.8	

73±17% for eroded plaque. The maximal percent coronary artery stenosis was 84±10% in coronary deaths of women >50 years of age and 78±16% in women ≥50 years of age (*P*>0.1).

The 26 acute thrombi were located in proximal segments in 16 hearts (62%): proximal left anterior descending before first diagonal (10), proximal right before the first large branch or acute angle (5), and proximal circumflex before the obtuse marginal (1). Eight thrombi were in the mid portion of the left anterior descending (5) or right coronary (3); one thrombus was in the distal right. At the site of thrombus, the percent stenosis was 66±15% in women ≥50 years of age and 79±7% in women >50 years of age (*P*=0.02) and was 77±8% for plaque ruptures and 70±16% for plaque erosions (*P*>0.1). Thirteen (50%) of the thrombi were occlusive; 8 (80%) of those in women >50 years of age and 5 (19%) of those in women <50 years of age were occlusive (*P*=0.04). Six of 18 (33%) of eroded versus 7 of 8 (88%) of plaque ruptures were occlusive (*P*=0.02).

### Vulnerable Plaques and Risk Factors

The mean numbers of vulnerable plaques were associated with TC (*r*<sup>2</sup>=0.3, *P*=0.002), increasing age (*r*<sup>2</sup>=0.3, *P*=0.002), and increased glycohemoglobin (*r*<sup>2</sup>=0.2, *P*=0.05) by univariate analysis. When risk factors of hypercholesterolemia (TC >210 and TC/HDL-C >5), diabetes (glycohemoglobin >10), and age (>50 years) were considered as categorical variables, vulnerable plaques were more numerous in hearts from patients with increased age (*P*<0.0001) and abnormal TC and TC/HDL-C (Table 4). By multivariate analysis, age >50 years and cholesterol were independently associated with numbers of vulnerable plaques (*F*=10.34, *P*=0.002; *F*=12.36, *P*=0.007, respectively). When age was used as a continuous variable, its association with mean numbers of vulnerable plaques was weaker (*F*=4.4, *P*=0.04). Other risk factor variables were not associated with vulnerable plaques (*P*>0.15 for all).

## Discussion

### Current Study

This study demonstrates that in women who die suddenly with severe coronary disease, traditional risk factors and menopausal status affect the mechanism of sudden death and coronary artery thrombosis found at autopsy. Because the majority of acute coronary thrombi caused by plaque erosion occur in young female smokers without significantly elevated cholesterol levels, body mass index, or glycohemoglobin levels, it appears that smoking cessation is the most important risk factor modification indicated for this group. In older women who are hypercholesterolemic, plaque rupture plays an important role in the development of acute coronary thrombosis, underscoring the need for cholesterol reduction in women who are postmenopausal. Plaques vulnerable to rupture were far fewer in younger women who died of severe coronary artery atherosclerosis than in postmenopausal women, indicating that the development of the substrate for plaque rupture appears to be inhibited in premenopausal women.

Sudden coronary death in the setting of healed myocardial infarction without acute coronary thrombosis constituted 35% of coronary deaths in this study. Therefore, a reduction in sudden coronary deaths in women would need to target that group of patients as well. Similar to women with plaque rupture, they are likely to be significantly older than women with plaque erosion. In addition, these women were more likely to be diabetic or hypertensive, two risk factors more prevalent in older women in our study. Therefore, control of hypertension and blood glucose levels may reduce sudden deaths in women with known coronary disease and a history of ischemic heart disease.

In addition to establishing a correlation between risk factors and mechanism of sudden coronary death in women, this study also demonstrates age-related differences in percent luminal stenosis at the site of thrombus and extent of coronary disease. In younger women who died of severe coronary disease, the mean degree of narrowing by atherosclerotic plaque at the site of thrombus was only 66% cross-sectional area luminal narrowing (equivalent to 43% diameter luminal narrowing), and there were relatively few narrowed segments of coronary arteries compared with women >50 years of age. The implication of this finding is that angiography in younger women may underestimate potentially lethal coronary artery narrowings in younger women.

Although this study demonstrates a clear association between traditional risk factors and type of coronary plaque morphology in women who die suddenly, not all women showed these associations. Seven (14%) died of stable plaque without infarct; this group showed no association with known risk factors. Furthermore, not all women with erosions were smokers and not all women with healed infarcts and stable plaque had evidence of either hypertension or diabetes. Therefore, it appears that other nontraditional risk factors for atherosclerosis may independently affect plaque morphology or interact with traditional risk factors. There is an evolving list of newer risk factors that have been implicated in

coronary atherosclerosis, including clotting factors such as plasminogen activator inhibitor, fibrinogen, von Willebrand factor antigen, and platelet glycoprotein IIb/IIIa gene polymorphism and lipid variants such as apolipoprotein E polymorphism and lipoprotein(a). The possible association of these risk factors with coronary plaque morphology are unknown<sup>16</sup> and have not been addressed in this study. Inflammation has been identified as a key component of plaque instability in both ruptures and erosions,<sup>19</sup> suggesting that local inflammation may be a mediator of acute thrombus with various underlying stimuli. However, the degree of inflammation in plaque erosion, as assessed by numbers of macrophages and lymphocytes, is significantly fewer compared with plaque rupture at the site of thrombosis in our previous study.<sup>20</sup>

### Sex Differences in Coronary Thrombosis

The current study demonstrates both similarities and differences between men and women in the relation of acute thrombosis and coronary risk factors. The link between hypercholesterolemia and plaque rupture appears to occur only in women who are postmenopausal; age does not appear to have an effect on this relation in men.<sup>14</sup> In addition, in women TC is specifically associated with plaque rupture, whereas in men, elevated TC/HDL-C is a predictor of plaque rupture. Because of the apparent protective effect of estrogen on plaque rupture, erosions are more common in women than in men.<sup>20</sup> Furthermore, there appears to be a stronger link between diabetes and hypertension and sudden death caused by stable plaque with healed myocardial infarction in women than in men, for reasons that have yet to be explored.

### Mechanisms of Sudden Coronary Death in Women

This study does not address possible cellular mechanisms that explain the association between risk factors and plaque morphology. The link between plaque rupture and elevated cholesterol levels may be explained by increased numbers of lipid-rich macrophages infiltrating fibrous caps, resulting in plaques vulnerable to rupture. The fact that premenopausal women appear to be protected in part from the effects of hyperlipidemia on the formation of vulnerable plaques suggests that estrogen may interfere with the accumulating of foam cells in coronary plaques, a hypothesis that has been supported by studies on nonhuman primates that demonstrate an inhibitory effect of estrogen replacement therapy on the uptake and degradation of LDL by the artery wall.<sup>15</sup> The mechanism of formation of eroded plaques is unknown but may be related to a propensity to thrombosis that is facilitated by components of cigarette smoke.<sup>20</sup> The apparent increased susceptibility of the chronically ischemic myocardium (healed infarction) to the development of fatal arrhythmias in patients with hypertension and diabetes, as shown in this study, may reflect microvascular disease that occurs in patients with diabetes and hypertension.<sup>21,22</sup> The mechanism of sudden death in women with stable plaques and healed infarcts probably is exacerbated by left ventricular hypertrophy because the hearts of women with stable plaques and healed infarcts were significantly heavier than other hearts in this study.

### Plaque Calcification and Extent of Luminal Narrowing

Previous autopsy studies have demonstrated that coronary artery lesions in young women contain less calcium and dense fibrous tissue than those of men and older women.<sup>23,24</sup> The degree of calcification in ruptured plaques, which in the current study were found predominantly in older women, has been demonstrated to exceed that of eroded plaques, which are more common in younger women.<sup>20</sup> Erosions also occur over plaques that result in a lesser degree of luminal narrowing, and this study demonstrated that the degree of arterial narrowing at the site of acute thrombus is less in young women than in older women. These data suggest that symptomatic coronary disease in young women may be angiographically less detectable, more likely to be missed on clinical evaluation, and more likely to be overlooked by ultrafast computed tomography.

### Limitations of the Study

The major limitation of this study is the inherent selection bias caused by autopsy sampling. It is noteworthy that larger numbers of sudden coronary death were seen in women <50 years of age, which is contrary to epidemiologic studies of sudden death in men as well as women. The most likely explanation for the large proportion of deaths in younger women is a higher autopsy rate of unexpected death in younger women without a history of heart disease. Deaths are investigated with complete autopsy at the medical examiner's office if there is no medical explanation of sudden death, which is more likely to occur in younger women without a prior history. However, this apparent bias is unlikely to effect the observation that in younger women, plaque rupture and vulnerable plaques are uncommon findings. These data support the hypothesis that the premenopausal state is protective against plaque rupture as a mechanism of acute coronary events.

### Conclusions

The mechanisms of sudden coronary death appear to differ in older women compared with younger women, and risk factors play different roles in these groups of patients. Young women who die of coronary artery thrombosis are often smokers with plaque erosions with relatively little coronary narrowing, whereas older women who die of coronary artery thrombosis are often hypercholesterolemic and have plaque ruptures with relatively severe coronary narrowing. The mechanism of sudden coronary death in hypertensive women and women with diabetes mellitus is often associated with healed myocardial infarcts and cardiomegaly. These data suggest that risk factor modification may be tailored to specific groups of women for the optimal reduction of sudden coronary death.

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