Risk factors and the anatomic distribution of coronary artery disease

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Abstract:
Differences in the importance of risk factors according to the anatomic location of coronary artery disease (CAD) were assessed in 4722 men and 1069 women who underwent arteriography. Examined characteristics included total and high-density lipoprotein (HDL)-cholesterol, triglycerides, obesity, smoking. Alcohol consumption, diabetes, and hypertension. Of these risk factors, the ratio of total to HDL-cholesterol showed the highest correlation with the overall severity of CAD *(r = 0.24,* men; *r = 0.38,* women); in contrast, its relation to left main (LM) disease was much lower (r =0.10, men; r = 0.08 women) than were correlations with stenotic disease in the left anterior descending, circumflex, and right coronary arteries. Other risk factors also showed weaker associations with LM disease than with stenoses in other vessels, and none was related to increased LM disease after controlling for disease in other vessels. For example, as compared with men who had no significant CAD, those with 1-, 2-, and 3-vessel disease had mean increases in total cholesterol of 12, 18, and 19 mg/dl, respectively. In contrast, after adjusting for disease in other vessels, LM disease (present in 293 men) was associated with only a 4 mg/dl increase in mean cholesterol levels *(P = 0.20).* These results indicate that the relation of risk factors to CAD differs according to the location of the stenotic disease, and that LM disease is poorly predicted by the standard risk factors.
Key words: Arteriography, Coronary artery disease, Lipids, Cigarette smoking, Left main disease

Article:
Introduction
The relation of risk factors to arteriographically-documented coronary artery disease (CAD) agrees well with findings of prospective studies of clinical disease. Despite possible selection biases [1], diabetes, cigarette smoking, alcohol intake, hypertension, and levels of lipids and lipoproteins have been related to CAD [2-6]. In addition, the importance of apolipoprotein levels was first demonstrated by arteriography [6,7], with results later confirmed in population-based, family studies [8]. However, coronary arteriography provides the additional opportunity to examine the relation of risk factors to stenotic disease at various anatomic locations. It is possible that some risk factors may be most strongly related to stenotic disease in one coronary artery, whereas other characteristics may be more predictive of disease in other vessels.

Because of the clinical importance of left main (LM) disease, possible risk factors for disease in this coronary artery have received much attention [6,9-14]. Although LM disease has been related to hypercholesterolemia [10,13,14] and to decreased levels of high-density lipoprotein (HDL)-cholesterol [11], others have reported that risk factors are not predictive of stenosis in the LM coronary artery [9,12]. Methodologic problems may, in part, account for these disparate findings: although stenosis of the LM coronary artery is typically found in persons with disease in other vessels [9,15,16], most clinical studies of LM disease have not controlled for the severity of disease elsewhere. For example, Bloch et al. [10] found that while hypercholesterolemic patients showed a high prevalence of LM disease, they also had extensive disease in the circumflex (CFLX) and right coronary arteries; therefore, the independent relation of cholesterol levels to LM disease (in persons with comparable amounts of disease in other vessels) was not assessed. Possible differences in the relation of risk factors to disease in the left anterior descending (LAD). CFLX, and right coronary arteries have not been examined.

We have previously described the relation of several risk factors to the overall severity of CAD, as assessed by an occlusion score, in 2006 patients undergoing arteriography [2,3]. The current analysis of 5791 adults (18% female) examines the relation of risk factors (diabetes, hypertension, alcohol consumption, cigarette smoking, and plasma levels of triglycerides, total and HDL-cholesterol) to stenotic disease in each coronary artery. The objective was to determine if associations between I risk factors and stenotic disease differ according to the location of the lesion. Emphasis is given to possible differences in the relation of risk factors to LM disease vs. their relation to disease in other vessels (non-LM disease).

Methods

Population and disease status

The Milwaukee Cardiovascular Data Registry is a clinical database consisting of patients referred to selected Milwaukee hospitals (St. Luke's and Zablocki Veterans Administration Medical Center) for diagnostic coronary angiography. The current study is restricted to patients examined from 1972 to 1986, and who had recorded levels of both total cholesterol and triglycerides. Overall, 5791 white patients, ranging in age from 24 to 84 years, were included in the current analyses. (Blacks accounted for only 4% of all eligible patients and were therefore excluded.) Angina was present in 60% of the patients, and 45% reported a prior myocardial infarction.

Arteriograms were evaluated by a radiologist and cardiologist, without knowledge of risk factor data. Percentage reductions (0, 1-49, 50-74, 75-89, 90-99 and 100%) in lumen diameter due to the most severe stenosis in the LM, LAD, CFLX, and right coronary arteries were incorporated into an occlusion score indicating the overall severity of CAD. As previously reported [2,3], a scale used by Rowe et al. [17] was modified, with a score of 0 representing no stenosis of any vessel, and a score of 300 denoting total occlusion of the major arteries.

In addition to this overall occlusion score, clinically important disease was defined as a 50% or greater stenosis of any vessel, with the extent of non-LM disease ranging from 0 to 3. LM disease, treated separately in most analyses, was also considered significant if ≥50% narrowing was ob served. Similar results were obtained using ≥75% narrowing of any vessel as the definition of significant disease.

Risk factor information

Medical records and questionnaires, completed before catheterization, were used to obtain data concerning overweight, alcohol consumption, smoking, and histories of hypertension, angina, diabetes mellitus, and medication use. Persons were excluded from the current analyses if they reported use of oral contraceptives, sex hormones, thyroid or cholesterol-lowering medication, or had hypo- or hyperthyroidism. These restrictions eliminated 1112 patients, with persons using cholesterol-lowering drugs (n = 463) representing the largest category of exclusions.

Height and weight were used to calculate the body mass index (BMI, kg/m^2). A 5-point smoking scale, reflecting both frequency and duration of smoking (1: never smoked, 5: smoked 2 or more packs daily for 20 years) was calculated as previously described [2]. Usual alcohol intake (including beer, wine, and mixed drinks) was converted to ounces per week of absolute alcohol [3]. Although data on smoking history and alcohol intake were most likely to be missing, information concerning both behaviors was available for 5133 (89%) patients.

Following an overnight fast, blood samples were collected before angiography. Plasma levels of total cholesterol and triglycerides were measured using automated procedures [18-20] in a laboratory standardized (and monitored) by the Centers for Disease Control. Beginning in 1977, levels of HDL-cholesterol were measured using procedures employed by the Lipid Research Clinics [20]; HDL-cholesterol levels were available for 1268 persons. The ratio of total cholesterol to HDL-cholesterol was used as an estimate of the atherogenicity of each person's lipoprotein profile.

Statistical analyses

Within each sex, mean levels of selected characteristics were contrasted between patients with no significant CAD and those with ≥1-vessel disease. The distribution of stenotic disease in each coronary artery, expressed on a 6-point scale (0,1-49, 50-74, 75-89, 90-99 and 100%), was then examined, and the interrelationship of disease among the coronary arteries was assessed. Nonparametric statistics (Wilcoxon tests and Spearman rank correlation coefficients) were used in several analyses because the distributions of certain variables (e.g., extent of stenotic disease, alcohol consumption, and triglyceride levels) were skewed.

Associations between occlusive disease in each coronary artery and risk factors were then examined, and multivariate regression analysis [21] was used to assess whether the relation of any risk factor to occlusive disease differed according to the location of the stenosis. A strong contrast of LM vs. non-LM disease was consistently observed, and the independent relation of risk factors to LM disease was further assessed. Analysis of covariance was used to control for age and the extent of non-LM disease while examining the relation of each risk factor to LM disease. (The power of these tests to detect statistically significant differences in mean levels of risk factors was calculated [22].) Analyses were then restricted to men with 3-vessel disease, and mean risk factor levels were compared between patients with or without LM disease. Two-sided P-values are used in all analyses, and a P-value < 0.01 is usually used as the level of statistical significance.

Results

Selected characteristics were first compared between patients with CAD (50% narrowing of any coronary artery) and those without clinically significant stenotic disease (Table 1). Of the 3564 men with CAD, the mean number of stenosed vessels was 2.0, and 8% (n = 293) had disease in the LM. Among the 490 women with CAD, the mean number of stenosed vessels was 1.9 and 5% (n = 23) had LM disease. Of the patients without clinically important CAD, 843 men and 488 women had no observed narrowing of any coronary artery.

TABLE 1

MEAN LEVELS OF RISK FACTORS, BY SEX AND DISEASE STATUS

	Males		Females	
	CAD absent (n = 1158)	CAD present [a] (n = 3564)	CAD absent (n = 579)	CAD present [a] (n = 490)
Age (years)	54 ± 10 [b]	56 ± 9	54 ± 11	58 ± 9
Total cholesterol (mg/dl)	221 ± 49	237 ± 49	223 ± 48	251 ± 53
Triglycerides (mg/dl)	165 ± 104	198 ± 133	136 ± 82	183 ± 109
HDL cholesterol (mg/dl) [c]	41 ± 12	37 ± 9	49 ± 14	42 ± 13
Total/HDL-cholesterol [c]	5.3 ± 1.6	6.3 ± 1.8	4.8 ± 1.5	6.0 ± 1.9
BMI (kg/m²)	26.6 ± 3.6 **	26.5 ± 3.4 **	26.1 ± 5.7 **	26.1 ± 4.4 **
Alcohol consumption (oz/wk)	6.4 ± 8.2	5.2 ± 6.6	2.3 ± 4.5 *	2.1 ± 4.4 *
Ever smoked cigarettes (%)	76	82	47	61
Smoking history score	3.1 ± 1.4	3.5 ± 1.4	2.0 ± 1.3	2.5 ± 1.5
History of				
Diabetes (%)	5	11	6	13
Hypertension (%)	34	40	43	57
Angina (%)	48	63	56	71

[a] ≥ 50% occlusion in the left main, left anterior descending, circumflex, or right coronary arteries.
[b] Values are mean ± SD.
[c] Analyses restricted to patients with measured levels of HDL cholesterol: 262 men without CAD, 740 men with CAD, 138 women without CAD, and 128 women with CAD.
Unless otherwise specified, mean levels of all risk factors in the CAD vs non-CAD groups are significantly different (as assessed by Wilcoxon or chi-square tests) at the 0.001 level.
* $0.001 < P < 0.01$; ** $P > 0.01$.

With the exception of BMI, patients with CAD had adverse levels of all risk factors. Reported histories of diabetes mellitus showed the largest proportional difference between the 2 groups, with its prevalence increased more than 2-fold among patients with CAD. Levels of triglycerides showed the next largest difference between

patients with CAD and those free of clinically important disease: a 20% [(198-165)/165] difference in men and a 35% difference in women. Although weekly alcohol consumption in women showed a relatively small difference (0.2 oz) between CAD categories, this was due to a large number of nondrinkers. Median levels of weekly alcohol consumption among women were L3 (no CAD) and 0.6 (CAD) oz.

TABLE 2

DISTRIBUTION OF CORONARY ARTERY STENOSES IN PATIENTS UNDERGOING CORONARY ARTERIOGRAPHY

Sex	n	Vessel	Percent reduction in lumen diameter					
			0 [a]	1–49	50–74	75–89	90–99	100 (total occlusion)
Men	4 722	Left main	89 [b]	4	3	2	1	0.3 [c]
		Left anterior descending	29	13	11	13	20	14
		Circumflex	44	12	11	9	13	11
		Right	33	15	9	8	13	22
Women	1 069	Left main	96	2	0.9	0.6	0.3	0.4
		Left anterior descending	53	12	8	9	11	7
		Circumflex	69	10	6	6	6	3
		Right	60	11	6	5	8	10

[a] 18% of all men (n = 843) had no observed narrowing of any coronary artery; 46% of all women (n = 488) had no observed narrowing of any coronary artery.
[b] Values represent the percent of each sex with specified occlusion.
[c] Percentages below 1 are rounded to the nearest 0.1%.

Table 2 shows the distribution of stenoses in each coronary artery, and as expected, the LM showed the least involvement with atherosclerotic disease: a narrowing of ≥50% was seen in only 293 men and 23 women. In contrast, total occlusions were found most frequently in the right coronary artery, and 75-99% reductions in lumen diameter were most prevalent in the LAD coronary artery. Men had more stenotic disease in each vessel than did women.

The interrelation of disease among the 4 vessels was then examined (data not shown). Stenoses in the LAD, CFLX, and right coronary arteries were moderately correlated (r = 0.41 to 0.48). In contrast, LM disease showed a much weaker association (r = 0.15 to 0.18) with disease in other vessels. suggesting that risk factors for LM disease might differ from risk factors for non-LM disease. However, isolated LM disease was rare, occurring in only 17 of 1754 patients; 10% of those with 3-vessel disease had ≥50% narrowing of the LM coronary artery.

TABLE 3

ASSOCIATIONS [a] BETWEEN SELECTED RISK FACTORS AND OCCLUSION IN EACH CORONARY ARTERY

Sex	n	Coronary artery	Risk factor							
			Age	TC	Plasma triglycerides	HDL-C [b]	TC/ HDL-C [b]	BMI	Alcohol consumption	Smoking history
Males	4 722	LM	0.08	0.06	0.01 **	− 0.05 **	0.10	0 **	− 0.03 **	− 0.03 **
		LAD	0.07	0.10	0.08	− 0.11	0.13	− 0.02 **	− 0.06	0.03 **
		CFLX	0.11	0.10	0.08	− 0.09	0.16	0 **	− 0.07	0.06
		Right	0.06	0.14	0.17	− 0.20	0.24	− 0.01 **	− 0.08	0.11
		Overall [c]	0.11	0.15	0.13	− 0.20	0.24	− 0.02 **	− 0.09	0.08
Females	1 069	LM	0.10	0.07 **	0.10	0 **	0.08 **	0.04 **	0.03 **	0.01 **
		LAD	0.19	0.29	0.26	− 0.21	0.30	0.07 **	− 0.10 *	0.06 **
		CFLX	0.17	0.23	0.22	− 0.26	0.30	0.09 *	− 0.07 **	0.12
		Right	0.16	0.28	0.30	− 0.26	0.34	0.05 **	− 0.06 **	0.21
		Overall	0.23	0.32	0.32	− 0.27	0.38	0.08 **	− 0.09 *	0.16

Abbreviations: LM, left main; LAD, left anterior descending; CFLX, circumflex; TC, total cholesterol; HDL-C, high-denstiy lipoprotein cholesterol.
[a] Spearman correlation coefficients
[b] Correlations between coronary artery disease and both HDL-C and TC/HDL-C are restricted to 1002 males and 266 females.
[c] Based on a score, which ranges from 0 to 300, representing the overall severity of stenotic disease.
Except where noted, all correlation coefficients are statistically significant at the 0.001 level.
* 0.01 < P < 0.01; ** P > 0.01.

Associations between risk factors and stenotic disease (which was categorized into six levels as in previous analyses) are shown in Table 3. All characteristics, with the exception of alcohol consumption in females and BMI, were consistently related to non-LM disease. However, associations with LM disease were generally much weaker. (Similar differences in the relation of risk factors to disease in each vessel were seen if regression coefficients, rather than correlations, were examined.) In females, for example, HDL-cholesterol was not related to LM disease $(r = 0)$, whereas' correlations with disease in other vessels were all $\leq$-0.21. Multivariate analyses indicated that age, lipid levels (and the ratio of total to HDL-cholesterol), and smoking history were more strongly related to disease in the LAD, CFLX, and right coronary arteries than with LM disease $(P < 0.0001$ for all contrasts). In addition, most risk factors tended to be more strongly related to stenoses in the right coronary artery than to disease in other vessels, and this differential association was particularly evident for cigarette smoking. Although smoking in women showed correlations of only 0.01 and 0.06 for disease in the LM and LAD vessels, respectively, its correlation with stenosis of the right coronary was 0.21.

Similar differences in LM vs. non-LM disease were also seen for diabetes and hypertension (data not shown). Significant LM disease was found in 6% of both nondiabetics and diabetics, and in 5% of non-hypertensives vs. 6% of hypertensives. In contrast, as compared with non-diabetics, diabetics showed an increased prevalence of disease in the LAD (66 vs. 52%), CFLX (54 vs. 39%), and right (61 vs. 47%) coronary arteries. Although hypertension showed a less marked trend, patients who reported that they were hypertensive also tended to have a higher prevalence of stenotic disease in the LAD (56 vs. 52%), CFLX (43 vs. 38%), and right (50 vs. 46%) coronary arteries as compared with non-hypertensive patients.

TABLE 4

LEVELS OF RISK FACTORS ACCORDING TO NUMBER OF DISEASED VESSELS AND LEFT MAIN STENOSIS

Characteristic	Sex	Coronary artery disease					
		Non-LM disease [a]: No. of stenosed vessels				LM Disease [b]	
		0	1	2	3	No	Yes
n	M	1172	1078	1207	1265	4429	293
	F	582	205	143	139	1046	23
Total cholesterol (mg/dl)	M	222	+12 [c]	+18	+19 **	233	+4
	F	216	+19	+28	+40 **	245	−14
Triglycerides (mg/dl)	M	159	+33	+37	+36 **	191	−11
	F	153	+31	+43	+66 **	171	+32
HDL cholesterol [d] (mg/dl)	M	41	−4	−5	−6 **	38	−1
	F	49	−5	−9	−12 **	43	0
Total/HDL cholesterol [d] (mg/dl)	M	5.5	+0.9	+1.0	+1.1 **	6.1	+0.4
	F	4.9	+0.8	+1.3	+2.0 **	5.8	+0.2
BMI (kg/m^2)	M	26.5	+0.1	+0.1	−0.1	26.6	−0.2
	F	26.3	−0.5	−0.2	+0.9	26.2	+0.4
Alcohol consumption (oz/wk)	M	6.2	−1.0	−0.9	−1.8 **	5.5	−0.4
	F	2.2	0	−0.5	0	2.2	−0.1
Smoking history	M	3.0	+0.4	+0.3	+0.3 **	3.4	−0.2 *
	F	2.1	+0.6	+0.6	+0.5 **	2.4	+0.1

[a] Number of vessels (left anterior descending, circumflex, and right) with $\geq$ 50% narrowing.
[b] $\geq$ 50% narrowing of the left main coronary artery.
[c] Increase (or decrease) in mean levels as compared to persons with no significantly stenosed vessel.
[d] Number of men with 0-, 1-, 2-, 3- and LM-disease: 263, 242, 251, 246, and 54. Number of women with 0-, 1-, 2-, 3-, and LM-disease: 138, 65, 36, 27, and 4.
P-values for main effects (non-LM or LM disease) as assessed by analysis of covariance. * $P < 0.05$; ** $P < 0.001$.

The independent relation of risk factors to LIM disease was then assessed using analysis of covariance to control for age and the extent of disease in other vessels (Table 4). With the exception of BMI and alcohol consumption in females, all risk factors were again independently related to the number of (non-LM) diseased vessels. Furthermore, although most risk factors showed a dose-response relation with the number of diseased

vessels, none was associated with increased LM disease. For example, as compared with women free of CAD, mean levels of total cholesterol were 19 (235-216), 28, and 40 mg/dl higher in those with 1-, 2-, and 3-vessel disease. In contrast, after controlling for the extent of disease in the LAD, CFLX and right coronary arteries, LM disease was associated with a (nonsignificant) 14 mg/dl decrease in total cholesterol. Interestingly, although cigarette smoking was associated with an increased amount of non-LM disease, mean smoking scores were similar among patients with 1-, 2-, or 3-vessel disease. Furthermore, smoking was inversely related to LM disease: after adjusting for the extent of non-LM disease, men with LM disease reported smoking *fewer* cigarettes *(P* = 0.02). No association between smoking and LM disease was seen in women.

TABLE 5

MEAN LEVELS OF RISK FACTORS ACCORDING TO PRESENCE OF LEFT MAIN DISEASE IN MEN WITH 3-VESSEL [a] DISEASE

	% stenosis of LM coronary artery	
	0 (n = 1033)	≥ 75 (n = 64)
Age (years)	56 ± 8 [b*]	59 ± 9 *
Total cholesterol (mg/dl)	238 ± 49	243 ± 49
Triglycerides (mg/dl)	199 ± 140	175 ± 101
HDL cholesterol (mg/dl) [c]	36 ± 9	36 ± 7
Total/HDL cholesterol [c]	6.3 ± 1.6	6.4 ± 2.2
BMI (kg/m^2)	26.5 ± 3.5	26.1 ± 3.5
Alcohol consumption (oz./wk)	4.7 ± 6.3	4.5 ± 6.7
Smoking history	3.5 ± 1.3 *	3.0 ± 1.5 *
History of:		
Diabetes (%)	13	19
Hypertension (%)	41	41

[a] ≥ 50% narrowing of the left anterior descending, circumflex, and right coronary arteries.
[b] Values are mean ± SD.
[c] Restricted to 207 men without LM disease, and 10 men with LM disease.
* $P < 0.01$.

Risk factors for LM disease were further examined in men with 3-vessel disease (Table 5). (This analysis contrasted risk factor levels between men with no LM narrowing vs. those with 75% stenosis to reduce the possible effect of LM misclassification.) Although men with severe LM disease were slightly older, LM disease was not associated with adverse levels of any other characteristic. However, the inverse association between LM disease and cigarette smoking was again evident (P < 0.01), (A similar inverse association between LM disease and cigarette smoking, although not statistically significant, was also seen in men with 2-vessel disease.) Although only 9 women with 3-vessel disease also had ≥ 75% narrowing of the LM coronary artery (vs. 130 women without LM disease), similar risk factor levels were also observed in these 2 groups (data not shown).

Discussion

Although several studies have shown that risk factors for coronary heart disease are related to the overall severity of arteriographically-documented CAD, the current results indicate that the strength of these associations depends upon the location of the stenotic disease. Whereas levels of total and HDL cholesterol, triglycerides, and alcohol consumption are associated with disease in the LAD, CFLX and right coronary arteries, their associations with LM disease are weaker. Furthermore, because (1) risk factors are related to non-LM disease, and (2) the prevalence of LM disease increases in conjunction with disease in other vessels, even the relatively low correlations with LM disease are confounded by the extent of disease in other vessels. The current results show that if the relation of risk factors to LM disease is examined in persons with similar amounts of CAD elsewhere, risk factors are not predictive of stenotic disease in the LM coronary artery. Of the previous studies that examined LM disease [9-15], Crittin et al. [9] and Plotnick et al. [12] also reported that risk factors are only weakly associated with LM disease.

The prevalence of LM disease increases if disease is present in other vessels [9,15,16]: in the current analyses, LM disease was present in only 1% of patients who had no other diseased vessel, but in 10% of those with 3-vessel disease. Although it has been reported that patients with LM disease have high levels of total cholesterol [10,13,14], decreased levels of HDL-cholesterol [11] or an increased prevalence of diabetes [23], the possible effects of disease in other coronary arteries have usually not been considered [6,9,10,14]. The current results indicate that, independently of their associations with disease in other vessels, the standard risk factors, are not related to increased LM disease. Although the lack of association in women may be due to the small number with significant LM disease (n = 23), a substantial number of men (n = 293) had ≥50% narrowing of this vessel. Power calculations for the analyses presented in Table 4 indicate that there was more than a 95% chance of detecting a 10 mg/dl difference in mean levels of total cholesterol (or a 4 mg/dl difference in mean HDL-cholesterol levels) between men without and with LM disease.

Unexpectedly, cigarette smoking among men (but not women) was associated with less LM disease. The decreased prevalence of LM disease among male smokers has previously been, observed by Sugrue et al. [14], and needs further confirmation. However, because a similar association was not seen in females, this inverse association may be due to chance or a possible selection bias. Although it has been suggested [24,25] that cigarette smoking may lead to increased symptomatology and result in smokers with mild disease undergoing arteriography, other data show that smokers are not at increased risk for angina [26]. Alternatively, smokers with LM disease may have a high case-fatality ratio and therefore, would not have been included in the present study (see below). In addition to the inverse association with LM disease in men, cigarette smoking showed no association with stenotic disease in the LAD, and was most strongly related to disease in the right coronary artery. Speculatively, the inconsistent results of autopsy studies concerning smoking and raised atherosclerotic lesions [27] may be due to the differing relation of smoking to stenotic disease in each vessel.

However, in contrast to the current results concerning HDL-cholesterol, Pearson et al. [11] reported that among patients with 3-vessel disease, those with LM disease had decreased levels of this lipoprotein fraction. Although this association was statistically significant in men who were < 50 years of age (n = 66), less than a 2 mg/dl (nonsignificant) difference in mean levels of HDL-cholesterol was observed in older men (n = 103) and in women (n = 47); subsequent analyses also revealed that even in young men, HDL-cholesterol levels were most strongly related to non-LM disease [11]. A recent study [6] also reported that men with LM disease do not have decreased levels of HDL-cholesterol.

Although coronary arteriography is useful in examining the relation of risk factors to atherosclerotic disease, its inherent limitations should be considered. The current study was cross-sectional in nature, and it is possible that concurrent risk factors do not accurately reflect levels before clinical symptoms appeared. However, this type of misclassification would have uniformly reduced all associations, and it cannot explain the weaker relation of risk factors to LM (vs. non-LM) disease. In addition, although arteriography generally underestimates histologic findings [28] and stenoses in the LM coronary artery are difficult 10 quantify [29,30], others have reported that these lesions are among the most reproducible [31]. Despite this possible disease misclassification, risk factors were not related to LM disease even it severe (≥ 75%) LM narrowing was contrasted with 0% stenosis (Table 5). Consideration should also be given to the highly selected nature of persons undergoing coronary arteriography: for example, the survival of persons with LM disease is poor [32]. However, for a selection bias to have resulted in the weak relation of risk factors to LM disease, it would be necessary for adverse risk factor levels to have preferentially reduced the survival of persons with LM (vs. non-LM) disease.

Despite these possible limitations, the current study confirms the relation of risk factors to stenotic disease in the LAD, CFLX, and right coronary arteries. The documented poor prognosis of patients with LM disease, however, makes early identification of this subgroup important. Both the Veterans Administration [33] and European Coronary Surgery [34] studies have demonstrated that coronary bypass surgery can reduce the mortality in symptomatic patients with significant disease in this vessel. However, the current results indicate that the standard risk factors are not predictive of clinically important LM disease among persons who undergo

coronary arteriography. It is possible that hemodynamic forces [35], rather than the standard risk factors, are primarily responsible for disease in the LM coronary artery.

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