

# Sex-related differences in the angiographic results of 14 500 cases referred for suspected coronary artery disease

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**Objective** To investigate sex differences of angiographic results in patients undergoing coronary angiography for suspected coronary artery disease (CAD).

**Methods** We retrospectively assessed the coronary angiograms of 2840 women and 11 610 men from 1984 to 2003. We examined sex differences regarding the extent and topography of significant stenoses (SS) (i.e.  $\geq 50\%$  of the luminal diameter), the age of presentation, and the variation of the annual frequency of the angiographic findings across the study period.

**Results** SS were recorded in 1817 women and 9984 men (64 vs. 86%,  $P < 0.001$ ). Women were more likely to present with nonsignificant stenoses (i.e.  $< 50\%$  of the luminal diameter) or angiographically normal coronaries ( $P < 0.001$ ). In patients with SS, women had a higher chance to present with one-vessel ( $P < 0.001$ ) or peripheral branches ( $P < 0.05$ ) disease, whereas men were more likely to have two-vessel disease ( $P < 0.005$ ). Compared with men, women were less likely to exhibit SS in the right coronary artery ( $P < 0.001$ ), left circumflex ( $P < 0.01$ ), intermediate artery ( $P < 0.01$ ) and first obtuse marginal branch ( $P < 0.01$ ). No significant sex differences were recorded in the frequency of SS in the left anterior

descending artery. In patients aged from 31 to 60 years, SS were more common in men, whereas in patients 61–80 years of age SS were more common in women. The annual frequency of SS in women gradually increased throughout the study period.

**Conclusion** SS were less common in women, were found later in life, and were less likely to involve the right coronary artery, left circumflex, intermediate artery and first obtuse marginal branch than in men. *Coron Artery Dis* 19:9–14 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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## Introduction

Sex differences in coronary artery disease (CAD) form an issue of current debate, as results from previous studies are controversial and conflicting. Women have a 10-year advantage vs. men in the risk of death from CAD; however, this gap narrows with advancing age, as comorbid diseases increase [1]. In addition, women exhibit worse physical health after a coronary event and worse prognosis after revascularization [2,3]. The reasons for these discrepancies between the sexes remain unclear, as little is known regarding potential sex differences in the angiographic extent and localization of coronary stenoses.

In this investigation, we studied the sex differences regarding the prevalence of CAD among participants who underwent coronary angiography in our institution over a 20-year period. We also sought to describe sex differences in the extent and topography of significant coronary lumen stenoses  $\geq 50\%$ . We additionally examined the

age differences between the sexes for several angiographic results, as well as the variation of the annual frequency of the angiographic findings in men vs. women over the 20-year period.

## Methods

We assessed through our database and retrospectively analyzed the data of 14 450 consecutive patients (11 610 men and 2840 women) who underwent their first coronary angiography in our institution from 1 January, 1984 to 31 December, 2003 [4,5]. Angiography in all participants was performed as part of the investigation of suspected CAD. Diagnosis was confirmed by visual evaluation of all the angiograms by a single independent expert interventional cardiologist blinded to the patients' clinical and laboratory records. Age and sex of participants, as well as the angiographic results, were recorded and summarized. We classified angiographic results in three categories according to criteria used in previously published angiographic studies [6,7]: (i) significant

stenoses (SS) for one or more lesions causing a reduction of the coronary lumen diameter  $\geq 50\%$ , (ii) nonsignificant stenoses (NSS) for coronary lumen obstructions  $< 50\%$  and (iii) normal coronary arteries (NCA), referring to the angiographic absence of coronary obstruction. To describe the angiographic extent of SS, we categorized the lesions into five groups: (i) one-vessel disease, defined as the presence of a single lesion in the left anterior descending (LAD), the left circumflex (LCx), the right coronary artery (RCA) or the intermediate artery (INT); (ii) two-vessel disease, defined as lesions in two of the above vessels; (iii) three-vessel disease, defined as lesions in three of the above vessels; (iv) left main disease, defined as lesions in the left main coronary artery and (v) branches disease, defined as lesions in peripheral coronary branches only. The institutional medical ethics committee approved the study.

Categorical variables, including sex, angiographic results and localization of SS were summarized as absolute values and percentages. Comparisons between them were carried out using Pearson's  $\chi^2$  test and Fisher's exact test, and were expressed as *P* values and odds ratios (OR) with the corresponding 95% confidence intervals (95% CI). Age was the only continuous variable recorded and was summarized as the median along with the 25th and the 75th percentile of its distribution. Age differences between men and women were assessed with Student's *t*-test and Mann-Whitney test, as appropriate. A *P* value of less than 0.05 was considered statistically significant. The statistical analyses were performed using SPSS, version 12.0 (SPSS Inc., Chicago, Illinois, USA).

## Results

### Sex differences in angiographic findings

In this series, SS were recorded in 1817 out of 2840 women (64%) and 9984 out of 11 610 men (86%). NSS and NCA were recorded in 159 (5.6%) and 864 (30.4%) women, respectively, whereas the corresponding values for men were 466 (4%) and 1160 (10%). SS were more likely to be found in men compared with women ( $P < 0.001$ ), whereas women were more likely to present with NSS ( $P < 0.001$ ) and NCA ( $P < 0.001$ ) (Fig. 1a).

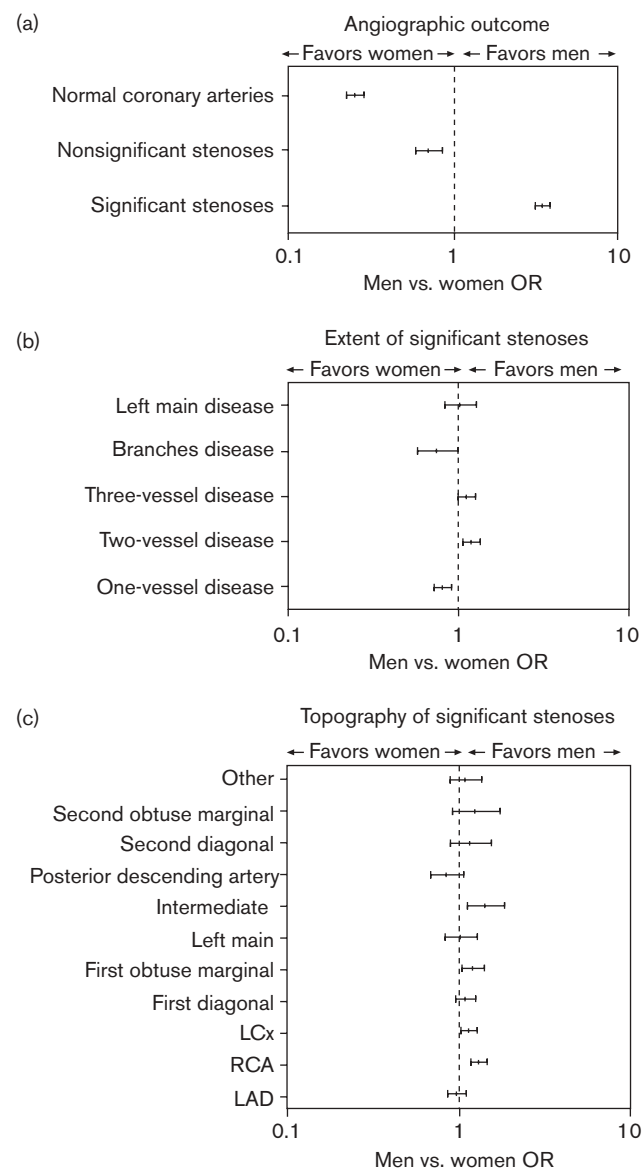
### Sex differences in the extent of significant stenoses

The extent of coronary stenoses in participants with SS is listed in Table 1. Women were more likely than men to have one-vessel disease ( $P < 0.001$ ) or peripheral branches disease ( $P < 0.05$ ), whereas there was a male predominance regarding two-vessel disease ( $P < 0.005$ ). No significant sex differences were recorded in three-vessel and left main disease (Fig. 1b).

### Sex differences in the topography of significant stenoses

The topography of coronary stenoses in participants with SS is listed in Table 1. Overall, SS most commonly

**Fig. 1**



(a) Men vs. women odds ratio (OR) plot for each angiographic result. Each point in the graph represents an OR, whereas the error bars correspond to its 95% confidence intervals (95% CI). An OR with 95% CI  $> 1.0$  indicates significantly higher likelihood for men, whereas an OR with 95% CI  $< 1.0$  indicates significantly higher likelihood for women. For all ORs  $P < 0.001$ . (b) Men vs. women OR plot for each category of significant stenoses (SS) extent. One-vessel and peripheral branches disease were more likely to occur in women, whereas two-vessel disease was more common in men. The remaining categories showed no difference across sexes. (c) Men vs. women OR plot for SS in each vessel. SS in the right coronary artery, left circumflex, first obtuse marginal branch and intermediate artery were significantly less likely to occur in women. LAD, left anterior descending; LCx, left circumflex; RCA, right coronary artery.

developed in the LAD, LCx and RCA in both men and women. Men were more likely to develop SS in the RCA ( $P < 0.001$ ), LCx ( $P < 0.01$ ), INT ( $P < 0.01$ ) and first obtuse marginal branch (OM1) ( $P < 0.01$ ). No significant

**Table 1** Angiographic characteristics of patients with coronary significant stenoses

Angiographic characteristics	Total (n=11801)	Men (n=9984)	Women (n=1817)	P
Extent of significant stenoses (%)				
One-vessel disease	3781 (32.0%)	3123 (31.3%)	658 (36.2%)	<0.001
Two-vessel disease	3805 (32.2%)	3274 (32.8%)	531 (29.2%)	<0.005
Three-vessel disease	3173 (26.9%)	2716 (27.2%)	457 (25.2%)	NS
Branch disease	338 (2.9%)	273 (2.7%)	65 (3.6%)	<0.05
Left main disease	704 (6.0%)	598 (6.0%)	106 (5.8%)	NS
Topography of significant stenoses (%)				
Left anterior descending artery	9033 (76.5%)	7634 (76.5%)	1399 (77.0%)	NS
Right coronary artery	7191 (60.9%)	6181 (61.9%)	1010 (55.6%)	<0.001
Left circumflex artery	5845 (49.5%)	4996 (50.0%)	849 (46.7%)	<0.01
First diagonal branch	2420 (20.5%)	2067 (20.7%)	353 (19.4%)	NS
First obtuse marginal branch	2145 (18.2%)	1855 (18.6%)	290 (16.0%)	<0.01
Left main coronary artery	704 (6.0%)	598 (6.0%)	106 (5.8%)	NS
Intermediate artery	642 (5.4%)	568 (5.7%)	74 (4.1%)	<0.01
Posterior descending artery	619 (5.2%)	511 (5.1%)	108 (5.9%)	NS
Second diagonal branch	486 (4.1%)	420 (4.2%)	66 (3.6%)	NS
Second obtuse marginal branch	356 (3.0%)	311 (3.1%)	45 (2.5%)	NS
Other coronary branches	721 (6.1%)	617 (6.2%)	104 (5.7%)	NS

sex differences were recorded in the frequency of SS in the LAD and the remaining coronary vessels (Fig. 3b).

### Sex differences in the age of presentation

The median age of presentation was 59 years [interquartile range (IQR) 52–65] for men vs. 62 years (IQR 57–67) for women ( $P < 0.001$ ). Men were significantly younger than women in the subpopulations with SS, NSS and NCA. Specifically, for SS, the median age for men was 59 years (IQR 52–65) vs. 64 years (IQR 59–69) for women ( $P < 0.001$ ). For NSS, the median age was 59 years (IQR 51–65) for men vs. 62 years (IQR 58–67) for women ( $P < 0.001$ ). For NCA, the respective values were 55 years (IQR 47–62) for men vs. 59 years (IQR 54–65) for women ( $P < 0.001$ ).

In terms of the age distribution of participants, men were more likely to present with SS from 31 to 60 years of age ( $P < 0.001$ ), whereas women were more likely to present from 61 to 80 years of age ( $P < 0.001$ ) (Fig. 2a and b). Men were more likely than women to be diagnosed with NSS between 31 and 50 years of age ( $P < 0.01$ ), while women were more frequently diagnosed with NSS at ages from 71 to 80 years ( $P < 0.05$ ) (Fig. 2c and d). NCA was more common in men at ages up to 50 years ( $P < 0.001$ ), and in women at ages from 61 to 70 years ( $P < 0.001$ ) (Fig. 2e and f).

### Variation of annual frequency of angiographic findings by time

The temporal course of the percentage of angiographies, as well as of men and women with SS, NSS and NCA, across the 20-year study period is shown in Fig. 3a, c, e and g, respectively. All entities showed a gradual increase over the years in both sexes. In the early years of our study, men were more likely to undergo angiography and present with SS, whereas angiography and SS were relatively more common in women towards the end of

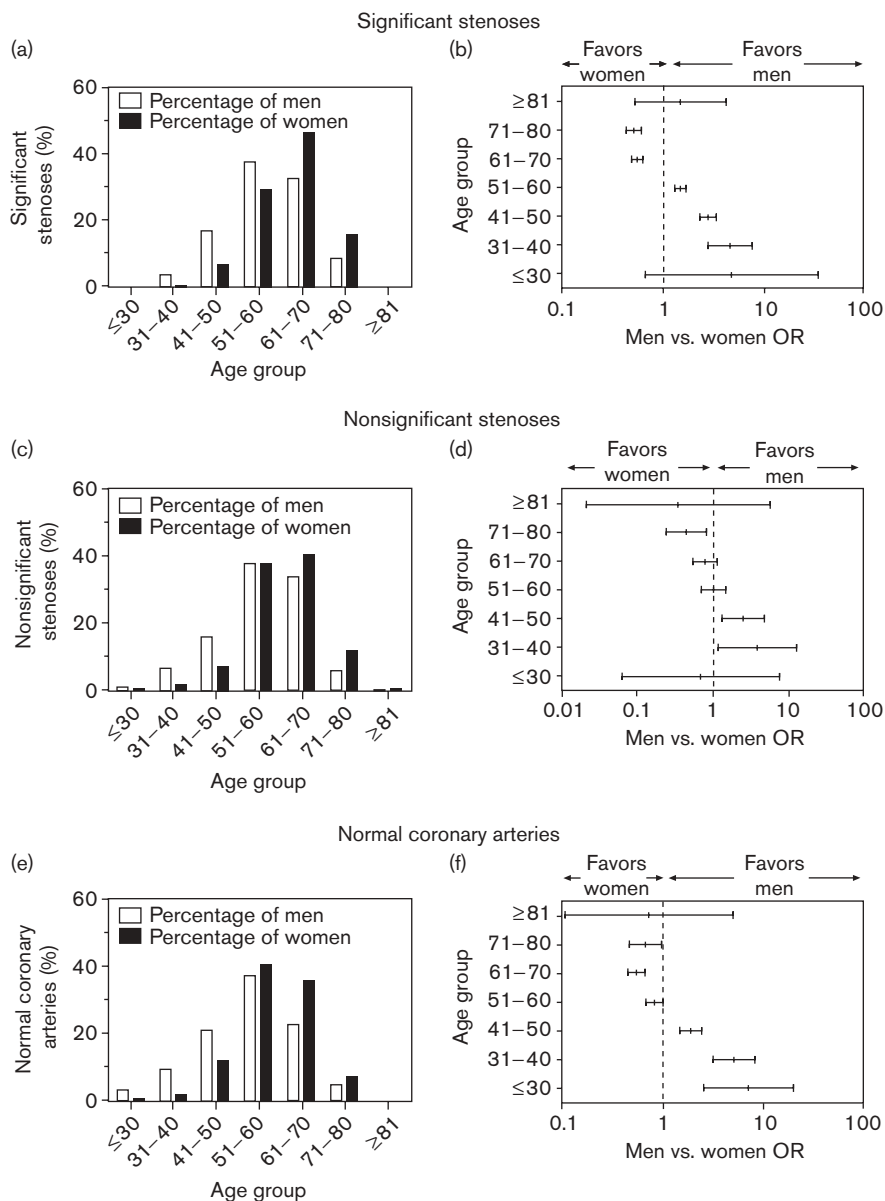
the study period (Fig. 3b and d). No significant sex differences were noted in the temporal trends of NSS and NCA (Fig. 3f and h).

### Discussion

We conducted an observational, retrospective, single-center study to evaluate the sex differences concerning the angiographic findings in a large dataset of 14450 patients who underwent coronary angiography as part of investigation of suspected ischemic heart disease during a 20-year period.

SS were less common in women. Our results regarding the lower probability of women to have angiographic SS and their higher likelihood to develop NSS or NCA are similar to those reported in the Coronary Artery Surgery Study [8] and other reports [9–11]. Recent data, however, suggest that the absence of obstructive CAD in women is not always benign and if accompanied by persistent chest pain, it is associated with adverse cardiovascular events [12]. Coronary microvascular dysfunction may account for this. As our participants underwent coronary angiography for suspected CAD, it is likely that they would have experienced chest pain. Another study reported frequencies of 43, 23 and 34% for SS, NSS and NCA, respectively, in a female population with suspected ischemic chest pain [13]. Of these values, the rate of SS was lower than ours and that of NSS higher, whereas for NCA there were no substantial differences in our findings. The different numbers of participants studied and possible differences in clinical indications for angiography may account for these discrepancies. Moreover, a higher angiographic threshold for measurement of a significant obstruction was used in some previous studies [9,11] and certain of the assessed patient samples [10,11] represent populations with different clinical probability of CAD in comparison with our population.

Fig. 2



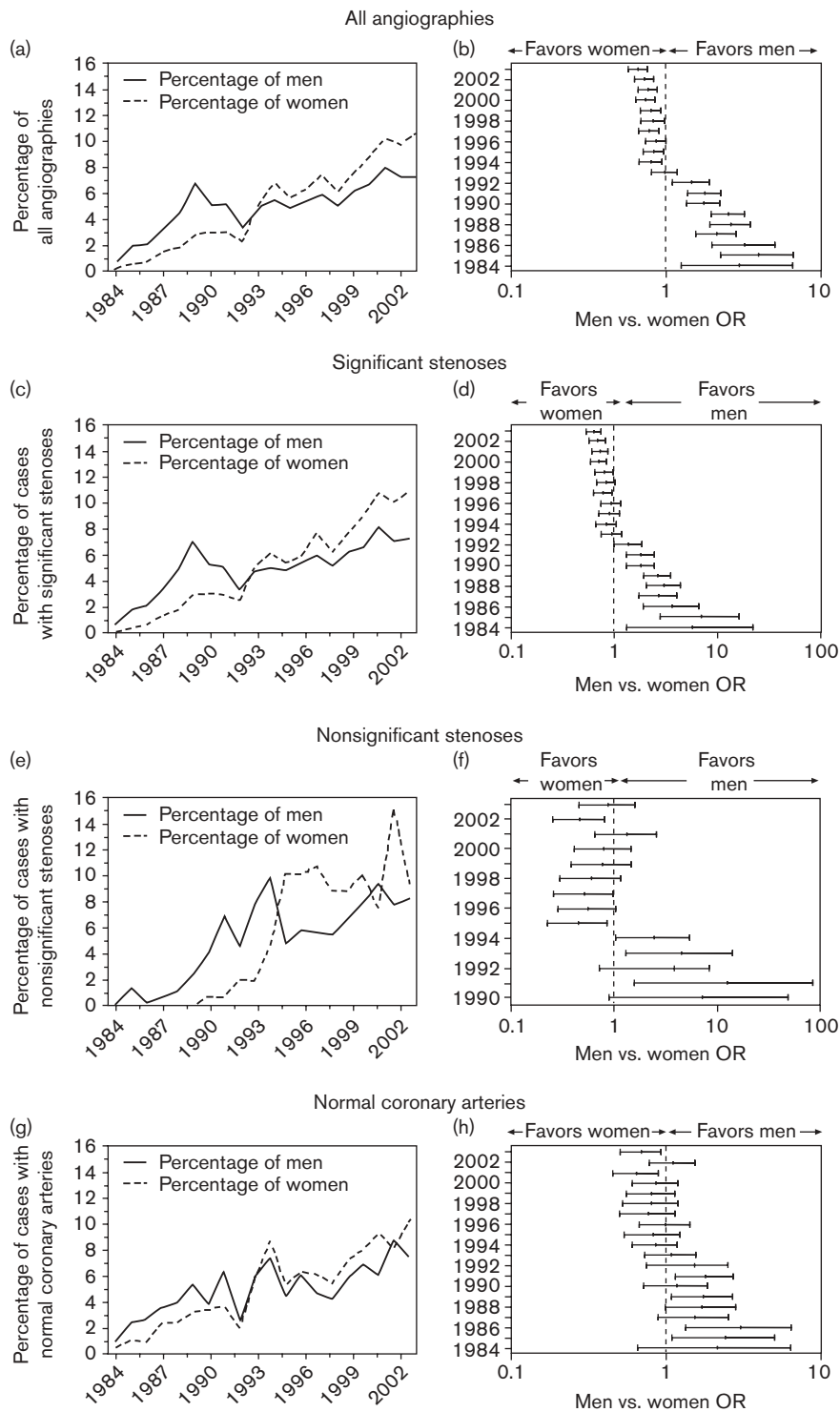
(a) Distribution of men and women with significant stenoses (SS) in different age groups. (b) Men vs. women odds ratio (OR) plot for SS in each age group. In age groups from 31 to 60 years, men were more likely to be affected ( $P < 0.001$ ). In age groups from 61 to 80 years, women were more likely to be affected ( $P < 0.001$ ). (c) Distribution of men and women with nonsignificant stenoses (NSS) in different age groups. (d) Men vs. women OR plot for NSS in each age group. At ages from 31 to 50 years, men were more likely to be found with NSS ( $P < 0.01$ ), whereas at ages from 71 to 80 years, women were more frequently affected ( $P < 0.05$ ). (e) Distribution of men and women with normal coronary arteries (NCA) in different age groups. (f) Men vs. women OR plot for NCA in each age group. Men were more likely to have NCA at ages up to 50 years ( $P < 0.001$ ), whereas women were more likely to have NCA at ages from 61 to 70 years ( $P < 0.001$ ).

In participants with SS one-vessel disease was more common to women, as was SS in peripheral branches, whereas two-vessel disease was more common to men. Previous studies, however, [9,10,14] showed no such sex differences. Disease in the RCA, LCx, INT and OM1 was less probable to occur in women, whereas no sex differences were noted in LAD disease. These findings regarding the anatomical distribution of CAD in women

are reported for the first time and need to be further confirmed in other populations.

Women were significantly older than men at the time of presentation, and this was observed in every angiographic result. This has also been reported before [9], and agrees with the universally accepted tendency for women to present with manifestations of atherosclerosis later than

Fig. 3



(a, c, e, g) Temporal course of the percentage of angiographies (a) and cases with significant stenoses (SS) (c), nonsignificant stenoses (NSS) (e) and normal coronary arteries (NCA) (g) by year of our study in men and women. (b, d, f, h) Men vs. women OR plot for angiography (b), SS (d), NSS (f) and NCA (h) in each year. In the early study years, men were more likely to undergo angiography and be found with SS, whereas angiography and SS were relatively more common to women toward the end of the study period. No significant temporal trends in sex frequencies were recorded for NSS and NCA. No women were recorded with NSS from 1984 to 1990; thus ORs could not be applied for that period.

men [15]. The increased prevalence of atherosclerotic coronary stenoses with the progression of age in both sexes has also been reported before in autopsy studies. The rate of this increase was, however, more prominent in men between 30 and 49 years of age, whereas a steady increase by age was encountered in women [16,17].

As for the temporal course of angiographic variables, they all showed an increase throughout the period our study covers. This may reflect a corresponding increase in the prevalence of cardiovascular disease over the years, or may be partially attributed to the gradual expansion in the workload of the hemodynamic laboratory in our institution, as part of the implementation of cardiac catheterization as a standard diagnostic modality for the evaluation of patients with suspected CAD. The increase in diagnostic angiography performed in women may also merely account for the increase in the likelihood of SS that was noted in women toward the end of the 20-year study period.

Several limitations within our study can be noted. First, it was confined to a specific population subgroup consisting of patients referred for coronary angiography; thus, the generalizability of our results to the general population is limited and the real prevalence of varying degrees of coronary obstruction in the community remains unknown. In addition, as it was conducted in a tertiary care center, many patients were examined upon referral and a referral bias regarding women cannot be excluded. Detailed information on the medical history of the participants was not available owing to heterogeneity of cases studied in terms of the cardiology center they were referred from, and also owing to the fact that no electronic patient records exist for the first years of the study. Moreover, the burden of CAD in human coronaries was based on data from conventional angiography, although newer imaging modalities, such as intravascular ultrasound, have proved more accurate in coronary imaging [18]. Finally, the unavailability of follow up data did not permit us to evaluate the long-term outcome of CAD in relation to sex.

In conclusion, this study attempted to provide an anatomic description of CAD in a large population of women referred for cardiac catheterization and to examine possible differences with the population of men studied over the same 20-year period. Overall, SS were less common in women, who presented more frequently with NSS and NCA. Women were older at presentation in all categories. Women had a higher likelihood to present with one-vessel and peripheral branch disease, and a lower chance to suffer from two-vessel disease. SS in women were less frequently localized in the RCA, LCx, INT and OM1 with no sex differences in LAD disease. In addition, the proportion of women undergoing angiography and being diagnosed with SS showed an increase over time. Further prospec-

tive studies would be needed to confirm the above findings and investigate factors that may account for these sex variations in coronary atherosclerosis.

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