Gender and Outcome in Patients with Coronary, Cerebrovascular or Peripheral Artery Disease. Findings from the FRENA Registry

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Abstract: *Background*: The influence of gender on the risk for subsequent ischemic events (i.e., myocardial infarction, stroke, critical limb ischemia) in patients with coronary (CAD), cerebrovascular (CVD) or peripheral artery disease (PAD) is not well known.

Patients and Methods: FRENA is an ongoing, observational registry of consecutive outpatients with symptomatic CAD, CVD, or PAD. We compared the incidence of subsequent ischemic events according to gender.

Results: As of July 2008, 2607 patients had been enrolled, of whom 713 (27%) were women. Women were significantly older and had diabetes or hypertension more often than men. Over a mean follow-up of 14 months, 228 patients (8.7%) developed subsequent events (myocardial infarction 72; ischemic stroke 76; critical limb ischemia 98). Of these, 37 (16%) were fatal. On univariate analysis, women had an increased incidence of subsequent ischemic events than men (odds ratio: 1.3; 95% CI: 1.0-1.8). On multivariate analysis, any influence of gender had disappeared. The most common type of subsequent event was one that was identical to the patient's initial manifestation, but women experienced events in the same vascular bed more often than men, particularly women initially presenting with CVD: 92% of women *vs* 62% of men with CVD had subsequent stroke (odds ratio: 6.5; 95% CI: 1.5-4.7).

Conclusions: Women had a higher incidence of subsequent ischemic events in the same vascular bed than men, particularly those with CVD. They also had a worse outcome than men, but this may be explained by the confounding effect of additional variables.

Keywords: Gender, arterial disease, outcome.

INTRODUCTION

Compared with the general population, patients with coronary artery disease (CAD), cerebrovascular (CVD) or peripheral artery disease (PAD) have an increased risk of both recurrence of the baseline event and of other manifestations of arterial disease [1-3]. However, there is little information on the risk of subsequent events (including myocardial infarction, stroke or critical limb ischemia) after an initial event. Previously published studies have reported rates of subsequent events that occurred during the patient's hospital stay, or have tended to focus on one atherosclerotic disease cohort and/or one subsequent event [4-10]. Other analyses examined cohorts selected for clinical trials, which may not be fully representative of the experience of the community [1, 11]. A better understanding of the pattern of recurrence of further vascular events may be helpful for better targeting of existing treatments.

Previous reports suggest that women developing CAD or CVD may have worse outcomes than men [12-15]. There are also data to suggest that gender differences may exist in the management of these patients, with men treated more aggressively than women [16, 17], but there is no reliable estimation of the influence of gender on the incidence of subsequent ischemic events.

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FRENA (Factores de Riesgo y ENfermedad Arterial) is an ongoing, multicenter, observational registry initiated in March 2003 to prospectively record the current clinical management and outcome of consecutive stable outpatients with symptomatic ischemic disease in the heart, brain, and/or major peripheral arteries in Spain [18, 19]. This study was done to assess the influence of gender on the incidence of subsequent ischemic events in a geographically defined population of stable outpatients with symptomatic CAD, CVD or PAD.

PATIENTS AND METHODS

Inclusion Criteria

Participating physicians prospectively enroll consecutive stable outpatients with symptomatic artery disease meeting at least one recent (<3 months prior to enrollment) episode of CAD (manifesting as angina or acute coronary syndrome); CVD (manifesting as transient ischemic attack or ischemic stroke); or PAD (either intermittent claudication with an ankle-brachial index <0.9, or previous vascular intervention or limb amputation for PAD). The Fontaine classification was used for categorisation of PAD [20]. All patients provide oral consent to their participation in the registry, according to the requirements of the ethics committee within each hospital.

Study Design and Definitions

The primary outcome was the incidence of subsequent ischemic events, defined as the composite outcome of acute myocardial infarction, ischemic stroke, or critical limb ischemia. Myocardial infarction was defined as a transient increase of CK-MB or troponin in combination with ischemic symptoms and/or typical electrocardiogram signs (development of pathologic Q-waves or ST-segment elevation or depression). Ischemic stroke was diagnosed if the patient had an appropriate clinical event not resolving completely within 24 hours, and had a brain CT or MRI that showed a compatible low-density lesion or was normal, or had findings compatible with hemorrhagic conversion of a cerebral infarct. Critical limb ischemia was considered in patients with intermittent claudication when presenting symptoms at rest (Fontaine stages III or IV). In PAD patients with stage III or IV, critical limb ischemia was considered when needing amputation. A patient was classified as having diabetes when there was a clinical history of diabetes or when they were taking insulin or oral antidiabetic agents. Patients were classified as having hypertension when there was a clinical history of hypertension or when they were taking antihypertensive medications. Creatinine clearance (CrCl) levels were measured according to the Cockcroft and Gault formula [21].

Follow-Up

A detailed history was performed on all patients at study entry (<3 months after an acute ischemic episode). Comorbid conditions were characterized, including a history of CAD, CVD or PAD, diabetes mellitus, hypertension, hyperlipidemia, chronic lung disease, chronic heart failure, cancer, and smoking status. Then, physical examination was performed comprising weight, height, heart rate and blood pressure on standard conditions, after 5 min of rest. An electrocardiogram was also recorded. After the initial visit, patients were followed-up at 3-month intervals. At these visits, medical history and data from physical examination were recorded, with special attention to risk factors; laboratory tests; lifestyle habits; the type, dose, and duration of treatment received, and outcome. Physicians were allowed to use any and all appropriate medications, as dictated by their usual clinical practice patterns.

Data Collection

The attending physicians ensure that eligible patients are consecutively enrolled. Data are recorded on to a computer-based case report form at each participating hospital and submitted to a centralized coordinating center through a secure website. Patient identities remain confidential because they are identified by a unique number assigned by the study coordinating center, which is responsible for all data management. Data quality is regularly monitored and documented electronically to detect inconsistencies or errors, which are resolved by the local coordinators. Data quality is also monitored by periodic visits to participating hospitals, by contract research organizations, who compare the medical records with the data in the web. A full data audit is performed at periodic intervals.

Statistical Analysis

Odds ratios and corresponding 95% confidence intervals were calculated for categorical variables. Incidence rates were calculated as both cumulative incidence and as person-time (events/100 patient-years). The significance of a number of clinical variables on the incidence of subsequent events was tested by a Chi-Square test for categorical variables. Candidate variables were selected from clinical variables based on published literature and on expert opinion. In order to measure predictors of outcome, a multivariate analysis was carried out using a Cox proportional hazard regression analysis. All analyses were completed with the Statistical Package for Social Sciences (SPSS) program (version 13.0. for Windows, 2004 SPSS Inc. Chicago, Illinois, USA), and a p-value <0.05 was considered statistically significant.

RESULTS

As of July 2008, a total of 2607 patients had been enrolled in FRENA, of whom 713 (27%) were women, 1894 (73%) men. Women were significantly older, weighed more, and had diabetes or hypertension more often than men, but were active smokers less frequently (Table **1**). They presented with CVD more often and with PAD less frequently. Among those with CAD, women presented with angina more often, with myocardial infarction less commonly. During follow-up, their mean levels of systolic or diastolic blood pressure were higher, and had atrial fibrillation more often. Their serum levels of CrCl were lower, those of cholesterol higher, and they received antiplatelet drugs or statins less often, but anticoagulants, calcium antagonists, ARA-II antagonists, diuretics, insulin or oral antidiabetics more frequently than men, as also shown in Table **1**.

Over a mean follow-up of 14 months, 228 patients (8.7%) had subsequent ischemic events: myocardial infarction 72; ischemic stroke 76; critical limb ischemia 98 (Table **2**). Across the three vascular disease cohorts combined, 180 (70%) subsequent events were the same type as that of the preceding event. In the CAD cohort, 83% of women *vs* 63%

Table 1. Clinical Characteristics, Risk Factors and Treatment Strategies of the 2607 Patients

	Women	Men	Odds Ratio (95% CI)	p Value
Patients, N	***713***	***1894***		
Clinical characteristics				
Age (years±SD)	71±11	65±12	-	<0.001
Body mass index (kg/m^2±SD)	29±5.2	28±4.1	-	<0.001
Underlying diseases				
Diabetes mellitus	336 (47%)	687 (36%)	1.6 (1.3-1.9)	<0.001
Hypertension	555 (78%)	1205 (64%)	2.0 (1.7-2.5)	<0.001
Current smoking	37 (5.2%)	422 (22%)	0.2 (0.1-0.3)	<0.001
Clinical presentation				
Coronary artery disease,				
Angina	123 (17%)	198 (10%)	1.8 (1.4-2.3)	<0.001
Myocardial infarction	145 (20%)	541 (29%)	0.6 (0.5-0.8)	<0.001
Cerebrovascular disease,				
Ischemic stroke	229 (32%)	411 (22%)	1.7 (1.4-2.1)	<0.001
Transient ischemic attack	99 (14%)	106 (5.6%)	2.7 (2.0-3.6)	<0.001
Peripheral artery disease,				
Intermittent claudication	95 (13%)	564 (30%)	0.4 (0.3-0.5)	<0.001
Symptoms at rest	24 (3.4%)	87 (4.6%)	0.7 (0.5-1.1)	N.S.
Artery disease in other beds	56 (7.9%)	183 (9.7%)	0.8 (0.6-1.1)	N.S.
Physical examination				
Mean SBP levels (mm Hg±SD)	140±17	136±22	-	<0.001
Mean DBP levels (mm Hg±SD)	76±9.4	75±9.3	-	0.022
Sinus rhythm	567 (82%)	1703 (92%)	0.4 (0.3-0.5)	<0.001
Mean serum levels				
Creatinine clearance (mg/dL)	58±23	76±29		<0.001
Total cholesterol (mg/dL)	190±35	178±36	-	<0.001
LDL-cholesterol (mg/dL)	112±31	108±30	-	0.002
Glucose (mg/dL)	122±41	118±38	-	0.026
Drugs				
Antiplatelets	606 (85%)	1744 (92%)	0.5 (0.4-0.7)	<0.001
Anticoagulants	162 (23%)	251 (13%)	1.9 (1.5-2.4)	<0.001
Beta-blockers	259 (36%)	758 (40%)	0.9 (0.7-1.0)	N.S.
Calcium antagonists	225 (32%)	456 (24%)	1.5 (1.2-1.8)	<0.001
Angiotensin II antagonists	291 (41%)	518 (27%)	1.8 (1.5-2.2)	<0.001
ACE inhibitors	307 (43%)	886 (47%)	0.9 (0.7-1.0)	N.S.
Diuretics	381 (53%)	660 (35%)	2.1 (1.8-2.6)	<0.001
Statins	512 (72%)	1461 (77%)	0.8 (0.6-0.9)	0.005
Insulin	148 (21%)	240 (13%)	1.8 (1.4-2.3)	<0.001
Oral antidiabetic agents	225 (32%)	469 (25%)	1.4 (1.2-1.7)	<0.001

Abbreviations: SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACE, angiotensin-conversive enzyme; CI, confidence intervals; NS, non significant.

of men had myocardial infarction (odds ratio: 2.7; 95% CI: 0.8-11); in the CVD cohort, 92% of women *vs* 62% of men had stroke (odds ratio: 6.5; 95% CI: 1.5-47); in those with PAD, 63% of women *vs* 70% of men had critical limb ischemia (odds ratio: 0.7; 95% CI: 0.3-1.7). Overall, women experienced subsequent events in the same vascular bed more often than men (odds ratio: 1.68; 95% CI: 0.92-3.12; p=0.046). Thirty-seven (16%) of the 228 patients with subsequent events died of the recurrent event (recurrent myocardial infarction 15, recurrent stroke 14, recurrent critical limb ischemia 8).

Overall, women had an increased incidence of subsequent ischemic events and an increased mortality, as shown in Table **2**. However, on multivariate analysis (after adjusting for gender, age, body mass index, initial presentation, diabetes, blood pressure levels, CrCl levels and prescribed drugs), only age >70 years, diabetes, initial presentation as PAD, and the use of anticoagulants were independently

Table 2. Clinical Outcome According to the Patient's Gender

	Women		Men		Hazard Ratio (95% CI)	P Value
	Events,* N (%)	Events Per 100 Patient-Years	Events,* N (%)	Events Per 100 Patient-Years		
All patients, N	***713***		***1894***			
Myocardial infarction	25 (3.5%)	3.1 (2.1-4.5)	47 (2.5%)	2.2 (1.6-2.8)	1.5 (0.9-2.3)	N.S.
Acute ischemic stroke	33 (4.6%)	4.2 (2.9-5.8)	43 (2.3%)	2.0 (1.4-2.6)	2.1 (1.3-3.3)	<0.001
Critical limb ischemia	21 (2.9%)	2.7 (1.7-4.0)	77 (4.1%)	3.5 (2.8-4.4)	0.8 (0.5-1.2)	N.S.
Any ischemic events	74 (10%)	9.6 (7.6-12)	154 (8.1%)	7.2 (6.1-8.4)	1.3 (1.0-1.8)	0.023
Death	45 (6.3%)	5.6 (4.1-7.4)	86 (4.5%)	3.9 (3.1-4.8)	1.4 (1.0-2.1)	0.027
CAD patients, N	***265***		***733***			
Myocardial infarction	19 (7.2%)	6.4 (4.0-9.8)	26 (3.5%)	2.9 (2.0-4.2)	2.2 (1.2-3.9)	0.006
Acute ischemic stroke	3 (1.1%)	1.0 (0.3-2.7)	7 (1.1%)	0.8 (0.3-1.5)	1.3 (0.3-4.9)	N.S.
Critical limb ischemia	1 (0.4%)	0.3 (0.02-1.6)	8 (1.1%)	0.9 (0.4-1.7)	0.4 (0.02-2.3)	N.S.
Any ischemic events	23 (8.7%)	7.8 (5.1-12)	36 (4.9%)	4.1 (2.9-5.6)	1.9 (1.1-3.2)	0.009
Death	15 (5.7%)	4.9 (2.8-7.9)	28 (3.8%)	3.1 (2.1-4.4)	1.6 (0.8-3.0)	N.S.
CVD patients, N	*313*		*510*			
Myocardial infarction	1 (0.3%)	0.3 (0.01-1.4)	5 (1.0%)	0.8 (0.3-1.8)	0.3 (0.01-2.5)	N.S.
Acute ischemic stroke	22 (7.0%)	6.3 (4.1-9.4)	23 (4.5%)	3.7 (2.4-5.5)	1.7 (0.94-3.1)	0.040
Critical limb ischemia	1 (0.3%)	0.3 (0.01-1.4)	9 (1.8%)	1.4 (0.7-2.6)	0.2 (0.01-1.2)	N.S.
Any ischemic events	24 (7.7%)	6.9 (4.5-10)	33 (6.5%)	5.4 (3.8-7.6)	1.3 (0.7-2.1)	N.S.
Death	20 (6.4%)	5.6 (3.5-8.5)	19 (3.7%)	3.0 (1.9-4.6)	1.9 (0.99-3.5)	0.028
PAD patients, N	***138***		***658***			
Myocardial infarction	5 (3.6%)	3.4 (1.3-7.6)	16 (2.4%)	2.3 (1.4-3.7)	1.5 (0.5-3.8)	N.S.
Acute ischemic stroke	8 (5.8%)	5.5 (2.6-10)	13 (2.0%)	1.9 (1.1-3.2)	2.9 (1.1-7.0)	0.013
Critical limb ischemia	19 (14%)	14 (9.0-22)	60 (9.1%)	9.0 (6.9-12)	1.6 (0.94-2.7)	0.034
Any ischemic events	27 (20%)	21 (14-30)	85 (13%)	13 (11-16)	1.6 (1.03-2.5)	0.019
Death	10 (7.2%)	6.8 (3.4-12)	40 (6.1%)	5.8 (4.2-7.8)	1.2 (0.6-2.3)	N.S.

* Some patients developed more than one major cardiovascular events.

Abbreviations: CAD, coronary artery disease; CVD, cerebrovascular disease; PAD, peripheral artery disease; CI, confidence intervals; NS, non significant.

associated with an increased risk for subsequent events (Table **3**). On the contrary, the use of statins was associated with a lower risk.

Table 3. Multivariate Analysis on the Risk to Develop Subsequent Ischemic Events

	Hazard Ratio (95% CI)	p Value
Clinical characteristics		
Age >70 years	1.3 (1.0-2.5)	0.037
Underlying diseases		
Diabetes	1.6 (1.1-2.2)	0.009
Initial clinical presentation		
Peripheral artery disease	2.0 (1.5-2.8)	<0.001
Drugs		
Anticoagulants	2.0 (1.4-2.9)	<0.001
Statins	0.7 (0.5-0.9)	0.005

Abbreviations: CI, confidence intervals.

DISCUSSION

Our data, obtained from a large series of consecutive outpatients with CAD, CVD or PAD, reveal that women experienced subsequent events in the same vascular bed (i.e., myocardial infarction in patients with CAD, stroke in those with CVD, critical limb ischemia in PAD) more often than men, particularly those presenting with CVD. This is a previously not reported finding, and may be helpful for better targeting of therapy and in devising effective new strategies for secondary prevention in these high-risk patients. In our series, one in every 7 patients with subsequent events died of the recurrent event. Thus, its clinical impact is considerable.

Our findings support the need for increased awareness among physicians of the amount of cross-risk that is related to overlap between the various locations of atherothrombosis, and the value of actively seeking out the presence of arterial disease in other beds if individual risk is to be more precisely assessed. The amount of cross-risk between arterial beds in patients with established disease has already been demonstrated in prior investigations, with a high risk of

recurrence of the index event and of other manifestations of atherothrombosis [2, 3, 7-11].

In addition, our data confirm that women with CAD, CVD or PAD have a worse outcome (i.e., an increased incidence of subsequent ischemic events and mortality) than men. The remarkable gender difference in patients with artery disease is still not completely understood [22-26]. Previous reports suggested that less aggressive management of risk factors in women may explain some of their worse outcome. In the present study, it may be explained by the confounding effect of additional variables, since women were older and had hypertension, diabetes or renal insufficiency more likely than men.

The FRENA registry provides insights into the natural history of artery disease with an unselected patient population, in contrast to the rigorously controlled conditions of randomized clinical studies. It can, therefore, help to identify factors associated with better or worse patient outcomes, and provide feedback from real-world clinical situations which may be valuable when designing new randomized clinical studies. Despite our efforts to control any bias from underlying diseases, it is likely that we were unable to eliminate such bias completely. Thus, the worse outcome found in women in this study may reflect pre-existing, unrecognized, disease processes, even after making careful exclusions. Furthermore, this study may include patients with third and later events and is not limited to patients with second events. Thus, this study is not strictly an analysis of the incidence of second events after an initial event within a cohort with established arterial disease, but it represents an analysis of subsequent events after an event first identified in the outpatient clinic. Finally, the follow-up time (average, 14 months) is short to draw firm conclusions. This study also has several strengths. To the best of our knowledge, this is the first time the prognostic importance of gender has been assessed in a large study of patients with CAD, CVD or PAD.

In summary, the results of our study suggest that women with CAD, CVD, or PAD have an increased incidence of subsequent ischemic events in the same vascular bed than men. Moreover, women had a worse outcome than men, but this may be explained by the confounding effect of additional variables.

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APPENDIX

Members of the FRENA Group

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