SCIENTIFIC LETTER

Long-term cardiac events in men and women with angina at rest and transient ST segment elevation

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Variant angina identifies angina at rest with transient ST elevation (ASTE) caused by coronary vasospasm in patients with non-significant coronary stenosis (<70%) and also in those with significant coronary stenosis (≥70%).^{1–4} In those with significant coronary stenosis, however, it is often uncertain whether angina is due to vasospasm, increased vasoconstrictive reactivity¹ or intermittent formation of platelet aggregates on an acutely complicated plaque, or a combination. Patients with ASTE may develop serious cardiac events such as myocardial infarction or sudden death,^{2–5} and although there are several series with follow-up^{2–4} only in one was it >6 years.² Thus, we analysed the long-term prognostic markers in patients with ASTE with emphasis on potential sex differences.

METHODS

Consecutive patients with ASTE (n = 364) from January 1984 to December 1999 were included. ASTE diagnosis was based on ≥1 episodes of ASTE (≥1 mm) without enzyme increase. Exclusion criteria were age >70 years, left bundle branch block, associated cardiac disease, previous myocardial infarction or coronary revascularisation. Severe coronary vasospasm was documented when ergonovine or intracoronary acetylcholine was given intravenously in patients with <70% stenosis. Cardiac death, myocardial infarction and sudden death were identified as main events; cardiac death was considered when following heart failure, myocardial infarction or coronary revascularisation, and sudden death when it occurred within 1 h of symptom onset. Analysis of variance or Wilcoxon rank sums test were utilised for continuous variables with normal or abnormal distribution, respectively. The Fisher exact test was used for categorical variables. Significant variables by univariate analysis were included in a regression analysis and Kaplan–Meier curves were plotted for different events.

RESULTS

Women were fewer (13% vs 87%) and older (mean (SD) age 60 (10) vs 54 (10) years, $p < 0.001$) than men and had a lower incidence of smoking (13% vs 86%, $p < 0.001$), a longer history of rest angina (526 (1054) vs 196 (465) days, $p < 0.001$), lower ST elevation (3.1 (3.4) vs 4.5 (4.4) mm, $p = 0.039$) and a higher incidence of <50% coronary stenosis (52% vs 26%, $p < 0.001$). During 106 (51) months in 363 (99.5%) patients, the incidence of rest angina in women and men was similar and was lower in patients with significant coronary stenosis than in those without (22% vs 50%, $p = 0.001$) due, in part, to the high revascularisation rate in patients with significant coronary stenosis (80%) and/or a different mechanism of angina. The incidence of death was comparable, but women showed a lower rate of cardiac death (4.3% vs 10.4%, $p = 0.284$) or myocardial infarction (2.2% vs 18%, $p = 0.004$; fig 1). Medical treatment in men and women was similar (calcium antagonists 64% vs 63%, $p = 1$; β -blockers 21% vs 33%, $p = 0.135$; aspirin 70% vs 67%, $p = 0.687$; statins 33% vs 44%, $p = 0.185$; and nitrates 42% vs

57%, $p = 0.188$). Moreover, the incidence of cardiac death or infarction was lower in women than in men with (2/22 (9.1%) vs 52/207 (25.1%), $p = 0.114$) or without significant coronary stenosis (0/24 (0%) vs 17/111 (15.3%) $p = 0.041$; fig 1).

Sudden death or recovered ventricular fibrillation or complete atrioventricular block occurred more often in patients with non-significant coronary stenosis than in those with significant coronary stenosis (19/135 (14.1%) vs 7/229 (3.1%) $p = 0.010$). Among those with non-significant coronary stenosis, it was lower in women than in men (0/24 (0%) vs 19/111 (17.1%) $p = 0.013$). In 21 of 26 (81%) patients, it occurred during the first 6 months of follow-up, and before the use of calcium antagonists in 17 (66%). Anterior ischaemia during angina was present in 28 of 35 (80%) patients with cardiac death, and patients with sudden death presented higher ST elevation than the rest (8 (5) vs 4 (4) mm, $p < 0.001$). Multivariate analysis showed multivessel disease (odds ratio (OR) 2.79 (95% confidence interval (CI) 1.4 to 5.4), $p = 0.004$) and tobacco smoking (4.4 (1.8 to 10.8), $p < 0.001$) as independent predictors for cardiac death and myocardial infarction, and coronary stenosis <70% (4.6 (1.5 to 14.1), $p < 0.001$) and tobacco smoking (4.6 (1 to 20), $p = 0.044$) as predictors for sudden death.

DISCUSSION

This study documents that women with ASTE presented a lower incidence of cardiac death, sudden death and myocardial infarction than men during nearly 10 years of follow-up. Moreover, women were represented in a much lower proportion and show apparent clinical and angiographic differences with men, features also not previously reported.^{2–5} Other observations of interest were that multivessel disease and tobacco smoking were the main independent predictors for cardiac death and myocardial infarction whereas coronary stenosis <70% and smoking were the main predictors for sudden death. Remarkably, women presented a low incidence of smoking but a similar incidence of other risk factors, suggesting that mechanisms of coronary vasoconstriction/spasm may differ from men.

The longer antecedent of angina at rest in women might relate, in part, to their delayed medical attention, but also to their higher incidence of non-significant stenosis and/or lesser tendency to coronary thrombosis. Despite notable improvement in the frequency of angina, nearly half of the women and men without significant coronary stenosis continued to experience episodes at rest at 8–10 years. This finding could partly be ascribable to a suboptimal control of their vasospasm, as suggested by its reproducibility in 18 of 20 patients during a repeated vasoconstrictive test at 105 months. Sudden death occurred mainly among patients without significant coronary stenosis and very rarely in women. Nakamura *et al*⁶ also

Abbreviation: ASTE, angina at rest with transient ST elevation

Figure 1 Left panels: Kaplan-Meier curves for the occurrence of myocardial infarction (MI) or cardiac death (CD) in patients with angina at rest with transient ST elevation (ASTE) showing a higher frequency of events in men than in women, with or without significant coronary stenosis. Right panels: incidence of sudden death (SD), ventricular fibrillation (VF) or complete atrioventricular block (CAVB) in patients with ASTE. It is apparent that men had a higher rate of events, particularly those without significant culprit coronary stenosis and during the initial months.

documented that 80% of patients with ASTE who died suddenly had non-significant stenosis although during a shorter follow-up—3.4 years—and in a Japanese population. One possible explanation is a larger ischaemic area as indicated by a higher ST elevation during angina than in patients without sudden death. The fact that sudden death occurred in two thirds of our patients before administration of calcium channel blockers stresses the protective role of coronary vasodilators.⁵

Our work reflects the continuum of patients with ASTE seen in a tertiary centre—from those with “normal” coronary arteries to those with critical stenosis—that imply a variety of mechanisms of coronary occlusion. Cardiac mortality, however, was low, 10% in men and 4% in women, over a long follow-up, which in part could be attributed to the increased revascularisation rate among patients with significant stenosis (80%) and the use of calcium antagonists, nitrates and aspirin.

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