Are we using cardiovascular medications and coronary angiography appropriately in men and women with chest pain?

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Aims The main purpose of the present study was to analyse the contemporary use of cardiovascular medications and diagnostic coronary angiography in men and women with suspected coronary artery disease (CAD). Furthermore, we examined the association of outcomes (death, myocardial infarction, repeat coronary angiography, procedural complications) with angiographic findings.

Methods All patients with stable chest pain (n = 12,200) referred for a first-time elective diagnostic coronary angiography during 2006–08 and registered in the Swedish Coronary Angiography and Angioplasty Register (SCAAR) were included. Significant CAD was defined as ≥50% luminal narrowing in any epicardial coronary artery.

Results In the youngest age group (≤59 years), more women than men (78.8 vs. 42.3%, P < 0.001) had normal/non-significant CAD, whereas more men had either left-main or three-vessel disease (18.2 vs. 4.2%, P < 0.001). Event rates were similarly low for men and women with normal/non-significant CAD, except for a higher procedural complication rate in women. Prior to angiography, fewer women than men with high-risk features were prescribed aspirin (83 vs. 86.1%, P = 0.001).

Conclusion In women, normal/non-significant CAD was highly prevalent, especially among younger women, and associated cardiovascular event rates were low. In men, findings of advanced disease were more common than in women, even younger men. Fewer high-risk women than men were initially prescribed aspirin. The observed sex differences suggest a need for improved identification of women appropriate for investigation with coronary angiography, earlier diagnostics in men, and heightened attention in the evidence-based use of aspirin in risk patients, especially women.

Keywords Chest pain • Coronary angiography • Gender • Aspirin

Introduction

Chest pain is one of the most common symptoms causing men and women to seek healthcare. The aetiology of chest pain includes a diversity of somatic diseases as well as psychological disorders. Exclusion of coronary artery disease (CAD) as the underlying cause is of cardinal importance given that ischaemic heart disease is a leading killer in both men and women globally. The diagnostic work-up in patients suspected of having CAD typically includes a first visit to a general practitioner who initiates medical therapy and refers the patient for non-invasive testing, followed by coronary angiography, which is considered the ‘gold standard’ for establishing the diagnosis of CAD.1 During this period, which may encompass several months, patients are often prescribed several cardiovascular medications, are given recommendations about limiting their physical activity, and some are even put on sick-leave.2 Also, the uncertainty of living with a suspected disease impacts negatively on the quality-of-life. Several studies

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have found that normal or non-significant CAD is much more common in women than men.\textsuperscript{3–8} This prompts the question of whether we are using coronary angiography appropriately, particularly in women with chest pain.

The main purpose of the present study was to analyse the contemporary use of first-time diagnostic coronary angiography in men and women with suspected ischaemic chest pain and without previously known heart disease. Furthermore, we examined the association of classical risk factors, use of cardiovascular medications and outcomes, to angiographic findings.

**Methods**

All patients with stable chest pain referred for a first-time elective diagnostic coronary angiography during 2006–08 and registered in the Swedish Coronary Angiography and Angioplasty Register (SCAAR) were included. SCAAR is a Swedish national registry that contains relevant medical data on consecutive patients from all hospitals in Sweden that perform coronary angiographies and percutaneous coronary interventions (PCIs). Patients with established CAD (i.e. previous MI, PCI, or coronary bypass surgery), heart failure, valvular disease, or arrhythmias were excluded.

Patients were divided into two groups according to the presence (men \( = 5029, \text{ women} = 1777\)) or absence (men \( = 2166, \text{ women} = 3228\)) of significant CAD, defined as \( \geq 50\% \) luminal narrowing in any epicardial coronary artery. The degree of stenosis was determined by the physician performing the angiography, based on the SCAAR registry definition (i.e. the percentage reduction in diameter as estimated by comparison with the diameter of the reference vessel). Information on risk factors was obtained through SCAAR. Hypertension and hyperlipidaemia were defined as patients currently on medical therapy for these conditions. The definition of diabetes included diet or medical treatment. Comorbidities and outcome measures were attained by merging the SCAAR database with the national patient registry, which includes information on patient hospitalization. Comorbidities included peripheral artery disease (PAD), stroke, chronic obstructive pulmonary disease (COPD), and cancer within the past 3 years. Outcomes included all rehospitalizations during the period 2006–08 for MI, any ischaemic event (International Classification of Diseases, Tenth Revision, codes I20 or I21), all-cause death, and repeat coronary angiography. The follow-up period differed for each patient, ranging from 1 day to 2 years, depending upon when the initial coronary angiography was performed. Procedural complications associated with the initial investigation included bleeding, stroke, allergy, or any vascular complication. Drug use 6 months before and 6 months after coronary angiography was obtained through a merging with the Swedish Prescribed Drug Register, in which information on drugs dispensed is available.

The study complies with the Declaration of Helsinki, and was approved by the local research ethics board.

**Statistical analysis**

All analyses were performed using SPSS version 18.0 (Chicago, IL, USA). Continuous variables were summarized as medians and interquartile ranges. Categorical variables were expressed as percentages. Comparisons among groups were made using the Mann–Whitney \( U \) test for continuous data and the \( \chi^2 \) test for categorical variables. Stepwise logistic regression modelling was used to determine predictors of significant CAD. The dependent variable was binary (normal/non-significant or significant CAD). Independent variables included age (per 10 years), sex, diabetes, hypertension, hyperlipidaemia, smoking (ever vs. never). Odds ratios and accompanying 95% confidence intervals (CI) were calculated. Analyses were carried out on all patients, and for men and women separately. The \( P \)-value of 0.05 was the threshold used in determining the level of significance. All tests were two-sided.

**Results**

**Distribution of findings at angiography**

During the period 2006–08, a total of 12,200 patients (men \( = 7195, \text{ women} = 5005\)) underwent coronary angiography. The proportion of women and men undergoing coronary angiography according to age was similar (Figure 1). The distribution of angiographic findings according to the severity of CAD and sex is shown in Figure 2. Normal/non-significant CAD findings were more common in women than men, which was true across all age groups (Figure 3). In the youngest age group (\( \leq 59 \) years), more women than men (78.8 vs. 42.3%, \( P < 0.001\)) had findings of normal/non-significant CAD, whereas more men showed findings of either left-main or three-vessel disease (18.2 vs. 4.2%, \( P < 0.001\)).

![Figure 1](image1.png) Proportion of patients undergoing first-time diagnostic coronary angiography according to age (years) and sex.

![Figure 2](image2.png) Distribution of vessel disease (VD) according to sex.
Risk factors
The distribution of risk factors and comorbidities is shown in Table 1. In patients with normal/non-significant CAD, the median age of women was higher and women had higher rates of hypertension, whereas more men were current or former smokers and had higher rates of diabetes. No sex differences were found regarding comorbidities in those with normal/non-significant findings. In general, patients with CAD were older and had higher rates of all risk factors and comorbidities than patients with normal/non-significant CAD. In patients with significant CAD, women were older and had higher rates of diabetes, hypertension, PAD, and COPD, whereas men were more often former smokers, and had higher rates of stroke and cancer. Rates of hyperlipidaemia did not differ between women and men in either group.

Risk factors associated with significant coronary artery disease
In a multivariate regression model including all patients, all of the classical risk factors (male sex, hyperlipidaemia, age per 10 years, diabetes, and smoking) were independently associated with significant CAD. The strongest association with significant CAD in women was diabetes and in men hyperlipidaemia (Table 2).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Risk factors and comorbidities according to presence or absence of significant coronary artery disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors/comorbidities (%)</td>
<td>Normal/non-significant CAD</td>
</tr>
<tr>
<td>Men, n = 2,166</td>
<td>Women, n = 3,228</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>61 (54–67)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13.5</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>11.3</td>
</tr>
<tr>
<td>Former</td>
<td>39.3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>47.6</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>48.6</td>
</tr>
<tr>
<td>PAD</td>
<td>1.2</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.9</td>
</tr>
<tr>
<td>COPD</td>
<td>5.2</td>
</tr>
<tr>
<td>Cancer (past 3 years)</td>
<td>2.2</td>
</tr>
</tbody>
</table>

PAD, peripheral artery disease. COPD, chronic obstructive pulmonary disease.

*Median (inter-quartile range).

P-value denotes comparison between men and women within groups.
Angiographic findings and outcome

During the 2-year period, event rates for death, rehospitalization for any ischaemic event, including MI and repeat coronary angiography, were similarly low for men and women with normal/non-significant CAD. All event rates were higher in patients with significant CAD, where MI and repeat coronary angiography were more frequent in women and all-cause death more common in men. In both groups, more women than men suffered procedural complications (Table 3).

Cardiovascular medication 6 months before and 6 months after coronary angiography

In patients with normal/non-significant CAD, both before and after coronary angiography more men than women were being treated with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), more women were being treated with beta-blockers and diuretics, and no sex differences were seen in the use of lipid-lowering medications or aspirin. After coronary angiography, there was a greater use of calcium antagonists in women only, whereas there was a greater use of ACE/ARBs, and lesser use of beta-blockers and aspirin in both men and women (Table 4).

In patients with significant CAD prior to coronary angiography, treatment with ACE-inhibitors or ARBs, beta-blockers, calcium antagonists, and lipid-lowering medications was similar for men and women, whereas more women than men were being treated with diuretics and more men than women being treated with aspirin. After coronary angiography, proportionately more women and men were being treated with all anti-hypertensive and lipid-lowering medications, and the use of aspirin was similar for men and women (Table 5).

Discussion

This study reports on the contemporary practice of an entire country in the use of first-time diagnostic coronary angiography, cardiovascular medications, and outcomes in the investigation of men and women with suspected ischaemic chest pain but no prior diagnosis of CAD. Several findings warrant discussion.

In Sweden, most stable patients referred for coronary angiography to rule out CAD undergo a diagnostic work-up that often involves physician evaluation, initially by a general practitioner, followed by non-invasive testing. Patients are thereafter referred to clinics performing coronary angiography where a specialist decides on whether or not further investigation is indicated. Despite this, we found that normal/non-significant CAD was much more prevalent among women than men, and especially common in younger women. These findings confirm, on a large scale, previous reports in the literature and bring to light the commonly addressed issue of the difficulty of diagnosing CAD in women.3–8 Compared with men, women more often report

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### Table 3 Outcomes

| Complication (%) | Normal/non-significant CAD | | | Significant CAD | | |
|------------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|
|                  | Men | Women | P-value | Men | Women | P-value |
| Myocardial infarction | 0.6 | 0.6 | 0.903 | 3.2 | 4.2 | 0.032 |
| Ischaemic event | 1.0 | 0.6 | 0.862 | 8.9 | 6.2 | 0.699 |
| Coronary angiography | 1.6 | 1.0 | 0.058 | 5.3 | 7.1 | 0.004 |
| Procedural complication | 1.1 | 1.8 | 0.030 | 2.9 | 5.9 | <0.001 |
| All-cause death | 0.4 | 0.3 | 0.862 | 1.1 | 0.6 | 0.036 |

P-value denotes comparison between men and women within groups.

### Table 4 Medical therapy 6 months before and 6 months after coronary angiography in men and women with normal/non-significant coronary artery disease

| Cardiovascular drug (%) | Six months before | | | Six months after | | |
|-------------------------|-------------------|----------------------------|----------------------------|----------------------------|----------------------------|
|                         | Men, n = 2166 | Women, n = 3228 | P-value | Men, n = 2161 | Women, n = 3225 | P-value |
| ACE/ARB | 36.1 | 32.0 | 0.002 | 39.3 | 34.3 | <0.001 |
| Beta-blockers | 60.5 | 65.9 | <0.001 | 51.0 | 55.7 | 0.001 |
| Calcium antagonists | 19.1 | 20.1 | 0.375 | 20.6 | 25.5 | <0.001 |
| Diuretics | 18.1 | 24.8 | <0.001 | 18.9 | 25.0 | <0.001 |
| Aspirin | 70.8 | 71.5 | 0.535 | 50.3 | 51.6 | 0.351 |
| Lipid lowering | 53.5 | 54.5 | 0.404 | 50.8 | 51.0 | 0.887 |

P-value denotes comparison between men and women within groups.
atypical symptoms, and in women non-invasive tests are less sensitive and specific, and risk factors have a different impact. All of these factors may contribute to problems in physician interpretation, leaving no other option than to proceed with invasive assessment.

Regarding outcomes in patients with normal/non-significant CAD, we found similarly low event rates in men and women for death, ischaemic events including MI, and repeat coronary angiography. The rate of procedural complications, however, was higher in women compared with men. Our findings, while congruent with some studies, contrast with others. Of importance is the distinction in the populations being studied. High cardiovascular event rates have been found in patients with acute coronary syndromes, in those with persistent angina symptoms and findings of endothelial dysfunction, and older patients in general with a greater risk factor burden. Low cardiovascular event rates are likely to be found in younger patients with atypical symptoms and a lower risk factor burden, in whom chest pain of non-cardiac origin is more probable. Hence, there appears to be a need for improvement in correctly identifying patients at high risk for future events; in low-risk patients (i.e. younger women in whom the prevalence of CAD is low), physician consideration of more likely differential diagnoses at initial symptom presentation could serve to limit inappropriate healthcare resource utilization. An exception which needs to be emphasized, however, is women with diabetes; diabetes, as found in our study and others, appears to be a most important risk factor in predicting significant CAD and increased mortality in women.

The finding of advanced obstructive CAD is much more common among men than among women. Although we did not have data on the duration of symptoms, patients in this study were those undergoing first-time diagnostic coronary angiography with no previous diagnosis of CAD (i.e. ‘de novo’ angina patients). Hence, this is a disturbing finding as it suggests a need for physicians to evaluate the continued use of aspirin in these patients more closely.

In patients with significant CAD, prior to coronary angiography the use of aspirin was less in women than in men, whereas the use of lipid-lowering medications was similar. The underuse of aspirin in women has been cited in other studies such as the Euro Heart Survey of stable angina and EUROASPIRE and may reflect physicians’ perceived lower risk in women. Medical management in these patients is reflective of the distribution of risk factors and present therapy traditions: more women than men had hypertension and were being treated with beta-blockers, calcium antagonists, and diuretics, whereas ACE/ARBs were more common in men.

After coronary angiography there was an increased use of all cardiovascular drugs in patients with significant CAD. Reasons for this may include previously untreated risk factors or need for more optimal therapy.

The use of aspirin specifically, in our patient cohort deserves attention. In patients with normal/non-significant CAD, we found that more than half of both men and women were still using aspirin 6 months after coronary angiography. Very few of these patients had other cardiovascular comorbidities. Findings from a recent meta-analysis of the use of aspirin in primary prevention suggest no clear benefit in the reduction in thrombo-occlusive events. On the other hand, an increase in bleeding events was found. This suggests a need for physicians to evaluate the continued use of aspirin in these patients more closely.

Limitations
A limitation of this study is that symptom descriptions and results of non-invasive tests were not available, meaning we were unable to identify how well patients met the specific criteria for referral for coronary angiography. Risk factor description was also limited to the data available in the SCAAR database, which, due to the definitions used, may underestimate the prevalence. In terms of angiographic findings, we were not able to separate...
patients with normal findings from mild CAD (i.e. 20–50% steno-
sis) due to the lack of more quantitative data in SCAAR. Regarding
outcomes, the only data we had available were for hospitalization
for ischaemic events that did not include the diagnosis of unspecific
chest pain, which has been shown to be a cause of resource con-
sumption in women particularly.2

Conclusions
Our findings suggest that, in our patient population, there was an
overuse of coronary angiography, especially in younger women.
Future studies need to focus on how physicians triage symptoms,
risk factors, and results of non-invasive tests in selecting patients
for coronary angiography. The finding of advanced CAD in men
undergoing first-time diagnostic angiography calls for an increased
awareness among men and research directed at uncovering plaus-
able explanations. Physician recognition of present therapeutic tra-
ditions for the continued use of aspirin in patients without significant CAD and tendency for underuse in women with high-
risk features needs to be improved.

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