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Health-related quality of life and outcome in atherosclerosis — Does sex matter?



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Cardiovascular disease (CVD) has a significant impact upon health-related quality of life (HRQOL) [1,2]. Over the years HRQOL has gained increasing attention and is currently being used in clinical trials as an outcome measure in patients with established CVD [3]. Poor HRQOL is associated with an increased risk of adverse cardiovascular events [4] and all-cause mortality [5]. Clinically, HRQOL may be a useful tool to help guide management strategies allowing for a more patient-focused approach. HRQOL has been found to differ between different CVD disease types [6] and also between men and women with CVD, with women more likely to report lower HRQOL [1]. The effect these cross-sectional differences have on the prognostic value of HRQOL is unclear. To investigate this we examined the sex-specific relationship between HRQOL and secondary cardiovascular events among coronary artery disease (CAD) and endarterectomy patients (both carotid and femoral [CEA and FEA]). All patients enrolled in the UCORBIO biobank [1] undergoing coronary angiography for CAD (n = 1880) and patients

in the Athero-Express biobank [7] undergoing CEA (n = 2023) or FEA (n = 804) were asked to complete the RAND-36 [8] HRQOL questionnaire (response rate 63% in Athero-Express patients). In addition the CAD patients also provided a EuroQol [9] self-rated health grade (response rate 73%). Questionnaires were filled in directly following the index procedure. Informed consent was obtained from each patient and the study protocols of UCORBIO and Athero-Express conform to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. Due to a profound non-response bias in HRQOL questionnaires [10], missing data was imputed for analysis (see Supplemental methods 1 for details about imputation) using the "MICE" package for R. Subsequently, a summary HRQOL score ranging from 0 to 10 was computed for analysis (HRQOL_{comp}) using the sex-specific regression coefficients of the RAND-36 parameters of the CAD patients for predicting the EuroQol health grade (see Supplemental methods 2). We evaluated the relationship between HRQOL_{comp} and major adverse cardiovascular endpoints (MACE, consisting of myocardial infarction, stroke, cardiovascular death, percutaneous coronary intervention, coronary artery bypass grafting, percutaneous transluminal angioplasty, peripheral arterial surgery and amputation due to arterial insufficiency) and all-cause mortality. We also tested for interactions between sex and HRQOL_{comp} for outcome in a multivariable Cox regression model. Covariates were determined ad hoc and consisted of sex, age, BMI, diabetes, hypertension, hypercholesterolemia, smoking, history of MI, history of CVA, history of PAD, eGFR, aspirin use, RAAS inhibitor use, statin use, diuretic use and beta-blocker use.

In concordance with the literature, we found that across the three disease groups, women reported lower HRQOL_{comp} than men (Table 1). During a median follow-up duration of 2.1 years (IQR = 1.3 to 2.9), 187 men and 60 women with CAD experienced a MACE and 86 men and 25 women died. Patients undergoing endarterectomy were followed up for a median duration of 3.0 years (IQR = 2.5 to 3.1), during which 329 men and 133 women undergoing CEA, and 242 men and 101 women undergoing FEA experienced a MACE. 166 men and 62 women

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Table 1
Baseline characteristics of FEA, CEA and CAD men and women.

| | CAD | | CEA | | FEA | | p |
|---|----------------|----------------|----------------|----------------|----------------|----------------|--------|
| | Female | Male | Female | Male | Female | Male | |
| n | 445 | 1435 | 650 | 1373 | 227 | 577 | |
| <i>Risk factors</i> | | | | | | | |
| Age (mean (sd)) | 67.7 (10.5) | 63.9 (10.6) | 69.6 (9.8) | 69.1 (8.9) | 68.0 (10.4) | 67.7 (8.9) | <0.001 |
| BMI (mean (sd)) | 27.1 (5.3) | 27.4 (4.1) | 26.3 (4.9) | 26.3 (3.5) | 25.1 (4.3) | 26.7 (9.3) | <0.001 |
| Diabetes (%) | 24.0 | 24.1 | 21.8 | 23.5 | 27.8 | 34.1 | <0.001 |
| Hypertension (%) | 69.4 | 56.9 | 78.8 | 72.0 | 73.1 | 71.2 | <0.001 |
| Hypercholesterolemia (%) | 44.9 | 48.9 | 66.9 | 67.0 | 64.8 | 66.9 | <0.001 |
| Smoking (%) | | | | | | | <0.001 |
| Non smoker | 52.6 | 44.3 | 23.4 | 11.1 | 8.4 | 4.0 | |
| Former smoker | 21.1 | 28.5 | 51.2 | 66.9 | 55.1 | 64.8 | |
| Active smoker | 26.3 | 27.2 | 25.4 | 22.0 | 36.6 | 31.2 | |
| eGFR (MDRD, mean (sd)) | 77.9 (25.5) | 86.2 (25.6) | 70.1 (21.3) | 73.8 (20.9) | 76.8 (33.4) | 83.4 (54.8) | <0.001 |
| <i>Medical history</i> | | | | | | | |
| History of MI (%) | 28.5 | 34.1 | 13.2 | 23.5 | 20.7 | 30.3 | <0.001 |
| History of coronary intervention (%) | 34.1 | 42.5 | 14.8 | 25.6 | 23.3 | 35.2 | <0.001 |
| History of CVA (%) | 9.2 | 10.0 | 82.5 | 81.3 | 15.4 | 14.9 | <0.001 |
| History of PAD (%) | 11.7 | 12.9 | 18.6 | 20.8 | 95.6 | 97.4 | <0.001 |
| <i>Medications</i> | | | | | | | |
| Aspirin (%) | 62.5 | 59.7 | 85.1 | 80.7 | 76.7 | 76.1 | <0.001 |
| P2Y12 (%) | 24.5 | 25.9 | 12.2 | 12.1 | 16.3 | 9.9 | <0.001 |
| RAAS inhibitor (%) | 51.2 | 52.5 | 48.9 | 51.6 | 53.7 | 64.8 | <0.001 |
| Beta-blocker (%) | 59.8 | 55.3 | 44.9 | 43.0 | 43.6 | 45.6 | <0.001 |
| Statin (%) | 60.4 | 65.5 | 77.4 | 75.5 | 71.4 | 72.1 | <0.001 |
| Diuretic (%) | 39.3 | 26.6 | 41.4 | 32.8 | 41.4 | 45.1 | <0.001 |
| <i>RAND-36</i> | | | | | | | |
| Physical functioning (median [IQR]) | 55 [35, 80] | 75 [50, 90] | 50 [25, 75] | 65 [40, 85] | 40 [25, 60] | 50 [30, 70] | <0.001 |
| Social functioning (median [IQR]) | 63 [38, 88] | 75 [50, 88] | 63 [38, 88] | 63 [50, 88] | 50 [0, 75] | 63 [25, 88] | <0.001 |
| Physical role functioning (median [IQR]) | 0 [0, 75] | 50 [0, 100] | 75 [0, 100] | 50 [0, 100] | 75 [25, 100] | 50 [0, 100] | <0.001 |
| Emotional role functioning (median [IQR]) | 100 [0, 100] | 100 [33, 100] | 33 [0, 100] | 0 [0, 100] | 67 [0, 100] | 0 [0, 100] | <0.001 |
| Mental functioning (median [IQR]) | 72 [56, 84] | 76 [64, 88] | 68 [52, 80] | 76 [56, 88] | 56 [16, 76] | 72 [48, 88] | <0.001 |
| Vitality (median [IQR]) | 50 [35, 70] | 60 [40, 75] | 50 [35, 70] | 60 [40, 75] | 40 [25, 65] | 55 [30, 70] | <0.001 |
| Pain (median [IQR]) | 67 [45, 100] | 78 [55, 100] | 77 [45, 100] | 88 [57, 100] | 45 [21, 57] | 51 [33, 78] | <0.001 |
| General health (median [IQR]) | 55 [35, 70] | 55 [40, 75] | 60 [50, 70] | 60 [50, 70] | 50 [40, 65] | 55 [45, 70] | <0.001 |
| Health change (median [IQR]) | 50 [25, 50] | 50 [25, 50] | 50 [25, 50] | 50 [25, 50] | 50 [25, 75] | 50 [25, 75] | 0.004 |
| <i>EuroQoL</i> | | | | | | | |
| QoL (mean (sd)) ^a | 6.5 (1.4) | 6.7 (1.5) | n/a | n/a | n/a | n/a | 0.006 |
| QoL _{computed} (median [IQR]) | 6.3 [5.1, 7.6] | 6.7 [5.3, 7.7] | 6.3 [5.0, 7.6] | 6.6 [5.0, 7.9] | 5.3 [2.9, 7.1] | 5.7 [3.9, 7.4] | <0.001 |

The p-value indicates the differences across all six groups; for categorical variables a chi-square test was performed, for normally distributed continuous variables ANOVA was performed and for non-normally distributed continuous variables a Kruskal-Wallis test was performed.

^a Only available for the CAD patients.

undergoing CEA, and 105 men and 52 women undergoing FEA died. Lower HRQoL_{comp} was significantly related to MACE among CAD, CEA and FEA patients, HR 1.17 [1.09–1.26], $p < 0.001$, HR 1.09 [1.03–1.40], $p = 0.001$ and HR 1.13 [1.07–1.16], $p < 0.001$ respectively. No significant sex interactions were found. Lower HRQoL_{comp} was also associated with all-cause mortality in CAD, CEA and FEA patients, HR 1.33 [1.20–1.49], $p < 0.001$, HR 1.08 [1.00–1.163], $p = 0.03$ and HR 1.17 [1.08–1.26], $p < 0.001$ respectively (Fig. 1). Once again no differences were found between men and women.

Our results highlight the predictive value of HRQoL with regards to MACE and all-cause mortality in CAD, CEA and FEA patients, with no differences found between men and women.

HRQoL not only significantly reflects a patient's wellbeing (socially, emotionally and physically) but it is also associated with cardiovascular outcome. Health care professionals must be encouraged to explore their patients' perceptions of their illnesses. Allowing patients to take a more proactive approach in the management of their own diseases could improve HRQoL.

To conclude; while women reported a poorer HRQoL than men, HRQoL predicted secondary cardiovascular outcome equally well in both women and men. HRQoL should be considered as an independent prognostic tool for the prediction of MACE and all-cause mortality in women and men with various types of atherosclerotic disease.

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Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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