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ARE LUTS AN INDEPENDENT INDICATOR OF CARDIOVASCULAR DISEASE (CVD) DEVELOPMENT? A CROSS-SECTIONAL AND LONGITUDINAL ANALYSIS IN MIDDLE-AGED TO ELDERLY MEN

Hypothesis / aims of study

Both lower urinary tract symptoms (LUTS) and cardiovascular disease (CVD) are conditions that are increasingly prevalent among ageing men. Recent studies have demonstrated that the two conditions share multiple risk factors (e.g. obesity, diabetes, hypertension, erectile dysfunction, smoking and alcohol consumption, and sedentary behaviour [1-3]). LUTS has consequently been suggested as a possible prognostic indicator of developing CVD in men, however the available longitudinal data remains equivocal.

This study aims to examine in a sample of community-based middle-aged to elderly men:

1) The cross-sectional association between LUTS (storage, voiding, and moderate-severe LUTS) on CVD both unadjusted and after adjustment for their shared factors;
2) The longitudinal association between LUTS (storage, voiding, and moderate-severe LUTS) on CVD incidence.

Study design, materials and methods

Subjects

Data were obtained from a cohort study of randomly-selected, representative men, aged 35-80 at baseline and living in the northern and western suburbs of Adelaide, South Australia [3]. Baseline clinic visits occurred between August 2002 and April 2005, with 5-year follow-up clinics held between August 2007 and September 2010. Data linkage for CVD events was obtained from study commencement until June 2015 through a state-wide registry of in-hospital events (emergency department visit or hospital separation).

Measures

Lower urinary tract symptoms (LUTS) and flow measurement: The International Prostate Symptom Score (IPSS) was used to assess seven items of urinary function: frequency, urgency, nocturia (storage LUTS), incomplete emptying, intermittency, weak stream, straining (voiding LUTS). Moderate- severe LUTS was defined as participants with a total IPSS score > 7. Maximum flow rate (volume-adjusted) was ascertained using uroflowometry for first morning voids.

Cardiovascular disease (CVD): CVD status was obtained by either self-report of physician diagnosis during clinic visits, or data linkage. Linkage CVD events were coded according to ICD-10 and included the following events: myocardial infarction, ischaemic heart disease, myocarditis, cardiomyopathy, cardiac arrest, heart failure.

Covariate data: Height, weight, waist circumference, DEXA, handgrip strength, and supine blood pressure measurements were collected as standard [3], with all plasma assays (triglycerides, HDL, LDL cholesterol, total testosterone, SHBG, PSA) performed in nationally accredited laboratories [3]. Information on demographics, smoking, alcohol, physical activity and disease status (incl: diabetes, depression, BPH, erectile dysfunction (ED)) was obtained by self-report questionnaire using validated measures [3]. Medication use was determined by self-report and data linkage with a national medication registry [3].

Statistical analysis

The cross-sectional analytic sample (n=1108) consisted of men who had a completed IPSS at baseline, and those without a history of bladder cancer (n=8) or prostate cancer (n=17) or prostate surgery (n=22) and those with a current self-reported urinary tract infection (n=5). For unadjusted models, exposure (moderate- severe, storage, and voiding LUTS) was fitted against outcome (CVD) using binomial logistic regression. Independents were first selected on the basis of demonstrated or suspected associations with the outcome/exposure. The longitudinal sample consisted of all those men of the initial sample who were CVD-free at T1 and attended follow-up visits (n=701). Cox proportional regression models were used to determine to hazard ratios (HR) for first-event CVD occurrence, with median time-to-event (in months) calculated using the Kaplan-Meier method with reversed event/censoring from clinical assessment until CVD event or date of data-linkage. To account for multiple testing, only independents with an unadjusted association with the outcome variable of $p<0.1$ were adjusted for age and then included in the final model if they demonstrated an age-adjusted association of $p<0.1$. To minimise co-linearity, covariates were only included when correlation coefficients ≤0.7. Assuming 10% CVD at baseline, the prevalence of a dichotomous predictor at least 25% and a variable inflation factor (VIF) of 20%, then with N=1100 there is 90% power to detect ORs of at least 1.2 in a logistic regression (2-sided alpha=0.05). With 130 CVD events and the same predictor prevalence and VIF assumptions, then there is 80% power to detect HRs of at least 1.85 in a Cox regression (2-sided alpha=0.05).

Results

For the cross-sectional sample, 9.4% (n=104) of men examined were found to have had CVD, most notably in men aged over 55 years. Men with moderate- severe, voiding, and storage LUTS were all found to have higher levels of CVD. There was no significant difference observed for PSA levels, volume-adjusted peak uroflow, or benign prostatic hyperplasia (BPH). In unadjusted binomial models, CVD was associated with moderate- severe LUTS (OR: 2.48; 95%CI: 1.61-3.81), storage LUTS (1.72; 1.14-2.60), and voiding LUTS (1.86; 1.12-2.89). There was no association detected between PSA, peak uroflow, or BPH. After adjustment for age, only moderate- severe LUTS (1.64; 1.04-2.59) remained significantly associated with CVD (storage LUTS: 1.24; 0.79-1.91 and voiding LUTS: 1.17; 0.73-1.86). In the multi-adjusted model, moderate- severe LUTS was independently associated with CVD (2.25; 1.29-3.95). Other significant associations included handgrip strength (0.94; 0.91-0.97), HDL (0.36; 0.14-0.96), diabetes (2.34; 1.26-4.36), and depression (2.02; 1.04-3.93).

In the longitudinal analysis, the mean follow-up duration was 73 months (range: 2-140 months). During follow-up, n=133 CVD cases (19.0% of sample; 24 MI, 38 IHD, 23 cardiomyopathy, 21 sudden cardiac arrests, and 27 heart failure cases) were detected. Of these, there was a higher proportion of men with moderate- severe (32.3% (n=43) with CVD vs 16.3% (n=92) without), storage

(38.3% (n=51) vs. 26.6% (n=151)), and voiding LUTS (36.1% (n=48) vs. 18.0% (n=102)). In unadjusted Cox proportional models, a significant unadjusted association was detected for moderate- severe LUTS (HR: 1.20; 95%CI: 1.03-1.74) and voiding LUTS (1.15; 1.03-1.50), but not storage LUTS (1.21; 0.85-1.72). After adjustment for age, moderate- severe LUTS (2.12; 1.26-3.85) and voiding LUTS (1.84; 1.23-3.71) were found to associate with incident CVD. In multi-adjusted models, both moderate- severe LUTS (3.11; 1.43-6.78) and voiding LUTS (2.46; 1.16-5.25) (separately inputted) were independent associated with incident CVD. Other independent associations included diabetes (2.16; 1.70- 5.93) and handgrip strength (0.98; 0.96-0.99).

Interpretation of results

We demonstrate in a group of broadly-representative, middle aged men an independent association between LUTS (both moderate- severe, and voiding symptoms) and the development of CVD. This effect was observed after adjustment for most known predictors of CVD in models of comparatively good fit (Nagelkerke $R^2$for IPSS>7 on incident CVD=0.184).

Differences with recent, similarly designed studies [1, 2] may be attributed to the inclusion of a larger number and wider variety of CVD events.

Further work is required to obtain additional prospective data in order to understand the specific associations between LUTS (e.g. LUTS severity and individual LUTS) and CVD in men. The utility of LUTS as a prognostic marker for CVD has important implications given men's apparent willingness to discuss urological function in the primary care setting.

Concluding message

Men presenting with moderate to severe LUTS or voiding symptoms should be strongly encouraged to address known CVD risk factors in addition to standard urological care, in order to prevent manifest CVD symptoms.

References

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Disclosures

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