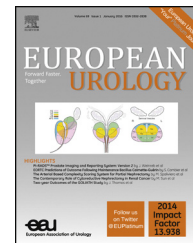


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Platinum Priority – Collaborative Review – Benign Prostatic Enlargement

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Male Lower Urinary Tract Symptoms and Cardiovascular Events: A Systematic Review and Meta-analysis

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Abstract

Context: The correlation among metabolic syndrome, lower urinary tract symptoms (LUTS), and cardiovascular disease (CVD) is well established. In particular, CVD has been proposed as a potential risk factor for both LUTS progression and severity.

Objective: To evaluate whether LUTS severity can be considered as a significant risk factor of major adverse cardiac events (MACE) in the male population.

Evidence acquisition: A systematic literature search was performed using PubMed, Google Scholar, and Scopus. The combination of the following keywords was adopted in a free-text strategy: *benign prostatic hyperplasia (BPH) or lower urinary tract symptoms (LUTS) and cardiovascular, cardio, major adverse cardiac events, MACE, heart disease, heart, myocardial infarction, myocardial, infarction, stroke, ischemic events, ischemic, cardiac death, coronary syndrome*. We included all cross-sectional and longitudinal trials enrolling men and comparing the prevalence or incidence of MACE in men with moderate to severe LUTS compared with those without LUTS or with mild LUTS. The studies in which only nocturia was evaluated were excluded from the analysis.

Evidence synthesis: Of 477 retrieved articles, 5 trials longitudinally reported the incidence of MACE in patients with moderate to severe LUTS in comparisons to those with mild or no LUTS and 10 studies reported the prevalence of history of MACE at enrollment. All were included in the present meta-analysis. Among cross-sectional studies, 38 218 patients and 2527 MACE were included in the meta-analysis. The mean age of enrolled patients was 62.2 ± 8.0 yr. Presence of moderate to severe LUTS significantly increased the risk of reported history of MACE ($p < 0.001$). Metaregression analyses showed that the risk of MACE was lower in older patients and higher in those with diabetes. The association between LUTS-related MACE and diabetes was confirmed in a multivariate regression model after adjusting for age (adjusted $r = 0.498$; $p < 0.0001$). Longitudinal trials included 25 494 patients and 2291 MACE. The mean age of enrolled patients was 52.5 ± 5.5 yr, and mean follow-up was 86.8 ± 22.1 mo. Presence of moderate to severe LUTS was associated with an increased incidence of MACE compared with the rest of the sample (odds ratio: 1.68; 95% confidence interval, 1.13–2.50; $p = 0.01$).

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Conclusions: Men with moderate to severe LUTS seem to have an increased risk of MACE. A holistic approach in considering the morbidities of aging men should be strongly encouraged and represents an important role for the practicing urologist.

Patient summary: We evaluated whether the severity of lower urinary tract symptoms could be considered as a significant risk factor for major adverse cardiac events (MACE) in the male population. We demonstrated that men with moderate to severe LUTS have an increased risk of MACE.

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1. Introduction

Lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH; LUTS/BPH) is one of the most frequently occurring urologic diseases in elderly men. Specifically, the incidence of moderate to severe LUTS in men aged >50 yr is 30–40% [1], with an increasing linear prevalence of LUTS with age [2]. Moreover, because of the global aging of Western populations, the cost burden associated with the management of LUTS will increase substantially over the next decades [3].

A noteworthy amount of preclinical and clinical evidence suggests a possible association among metabolic factors, metabolic syndrome (MetS), and male LUTS [4–6]. In particular, triglyceride and cholesterol levels seem to have a detrimental effect on prostatic cells, boosting prostate inflammation, which can be associated with the development and progression of LUTS/BPH [5]. Moreover, a recent meta-analysis demonstrated that obesity, dyslipidemia, and age are significant risk factors of having MetS as a determinant of benign prostate enlargement (BPE) [6]; therefore, LUTS seems to share a number of risk factors with cardiovascular diseases (CVDs). Accordingly, the European Association of Urology guidelines recognize the need to investigate these relevant comorbidities, including diseases, medications, and lifestyles [4]. Similarly, insulin resistance, dyslipidemia, and hypertension have been proven to be strong determinants of the development of CVD. In 2005, the American Diabetes Association and the European Association for the Study of Diabetes emphasized that each risk factor can cluster with others, leading to a single pathophysiologic conditions, defined as MetS [7]. In a recent meta-analysis on the cardiovascular risk associated with the MetS, including data from 87 studies and 951 083 patients, MetS was associated with a twofold increase in risk of CVD, CVD mortality, myocardial infarction, and stroke and a 1.5-fold increase in risk of all-cause mortality [8].

Because correlations between MetS and both LUTS and CVD have been proven, CVD has been proposed as a potential risk factor for LUTS progression. In addition, LUTS severity has been investigated as an early clinical manifestation of a larger subclinical systemic disorder that can progress in severe CVD.

Specifically, the Massachusetts Male Aging Study (MMAS), a population-based study of 1709 noninstitutionalized randomly selected men aged 40–70 yr, demonstrated that coronary heart disease can independently increase risk for development of clinical BPH over 9 yr [9]. In a recent cross-sectional longitudinal study investigating the association

between LUTS and both CVD and stroke in 2092 men aged 47 yr and followed for an average of 6 yr, Wehrberger et al reported that men with severe LUTS (International Prostate Symptom Score >20) are at increased risk of CVD and stroke (odds ratios [ORs] of 1.28 and 1.66, respectively) [10].

Several publications have corroborated evidence that CVD could be a risk factor for worsening LUTS, whereas other prospective trials have suggested that severe LUTS could be associated with a modest but significant risk of developing a CVD. The aim of the present systematic review is to investigate the correlation between LUTS severity and risk of major adverse cardiac events (MACE), defined as angina pectoris, acute myocardial infarction, other chronic ischemic heart disease, transient ischemic attack, or cerebrovascular accident.

2. Evidence acquisition

This meta-analysis was performed according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies [11]. Moreover, a Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist has been included as Supplementary Table 1.

2.1. Eligibility criteria

All studies that specifically evaluated the presence of MACE in patients with or without moderate or severe LUTS were included in the analysis. The following inclusion criteria were adopted: (1) The study reported original data and was published in a peer-reviewed journal (ie, not a meeting abstract or review article), (2) the study was a cohort study (prospective or historical cohort) consisting of male human adults or the male cohort data could be extrapolated from the paper, and (3) the authors reported the incidence or the prevalence of cardiovascular events in patients with and without LUTS.

For the definition of MACE, we used the International Classification of Primary Care (ICPC) definitions for CVDs, including K74, angina pectoris; K75, acute myocardial infarction; K76, other chronic ischemic heart disease; K77, congestive heart failure; K89, transient ischemic attack; and K90, cerebrovascular accident [12].

2.2. Information source and search strategy

An extensive search of Medline, Embase, and Cochrane was performed and included the following words: benign

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