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ORIGINAL ARTICLE

The cardiovascular risk factors in men with lower urinary tract symptoms

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Abstract

Objective It has been hypothesized that endothelial dysfunction and pelvic atherosclerosis may contribute to lower urinary tract symptoms (LUTS). We assessed the relationship between cardiovascular risk factors and LUTS severity in male patients presented to urology clinic.

Methods It is a cross-sectional study on patients who presented between 2013 and 2015 with LUTS. A total of 1176 male patients were encountered, and 966 were included for analysis after excluding patients with urinary tract malignancy, urethral stricture, bladder stone and history of urinary tract surgery. Cardiovascular risk factors including components of Framingham risk score, body mass index, uroflowmetry, International Prostate Symptoms Score, fasting blood glucose and serum prostate-specific antigen (PSA) were assessed. Correlation between Framingham risk score, cardiovascular risk factors and severity of LUTS was investigated.

Results Multinomial logistic regression analysis showed that severe LUTS significantly associated with Framingham score ($P=0.008$) and its components of total cholesterol (OR = 1.318; $P=0.010$) and age (OR = 1.032; $P=0.006$) compare with mild symptoms. Framingham risk score was found to correlate with storage symptoms (CC = 0.083; $P<0.0001$) but not voiding symptoms (CC = − 0.029; $P=0.185$).

Conclusions Severity of LUTS and storage symptom significantly increases Framingham risk score, particularly with the components of total cholesterol level and age.

Keywords Benign prostate hyperplasia · Cardiovascular risk · Lower urinary tract symptoms

Introduction

Lower urinary tract symptoms (LUTS) are common among middle-aged to elderly men [1]. Studies have been carried out to assess the implication of LUTS, trying to investigate the association of LUTS beyond the urinary system. The initial effort looked into the association of metabolic syndrome and LUTS, in view of a possible association with prostatic inflammation and metabolic syndrome [2]. While metabolic syndrome as a whole is an important determinant in both the development and progression of benign prostatic hyperplasia-related LUTS, the evidence for the associations is still conflicting for individual components of metabolic syndrome [3]. Bouwman et al. investigated the relationship between LUTS and major cardiovascular diseases [4]. In their cross-sectional analyses, they revealed a clear correlation. However, such correlation was not evident in their longitudinal analyses. On the other hand, a meta-analysis by Gacci et al. suggested a correlation between LUTS and major adverse cardiac events [5].

It is increasingly recognized that the aetiology of LUTS extends well beyond prostate enlargement and bladder outlet obstruction [6]. With the finding that there is a correlation between LUTS and cardiovascular diseases, it may be explained by the suggestion that both of them share similar risk factors such as obesity, hypertension, dyslipidaemia, and ageing. While the association of these cardiovascular risk factors with adverse cardiac events is well studied

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[7], the evidence on their relationship with LUTS is still inconclusive.

Framingham risk score was developed from the Framingham Heart Study, and initially was a gender-specific algorithm used to estimate the 10-year coronary heart disease risk of an individual [8]. The algorithm took into consideration the risk factors of age, smoking status, blood pressure, cholesterol level and the need of antihypertensive treatment. We investigated the correlation between LUTS and Framingham risk score, as well as other cardiovascular risk factors. By doing so, we aimed at having a more comprehensive understanding of the pathogenesis and implication of LUTS.

Methods

It was a cross-sectional study on male subjects aged 18 years or above, referred to a tertiary centre urology clinic for lower urinary tract symptoms, elevated prostate-specific antigen (PSA) or haematuria from January 2013 to September 2015. The primary end point of the study was urinary symptoms severity as determined by International Prostate Symptom Score (IPSS). Secondary end points include different domains of LUTS in correlation with cardiovascular risk factors. The study was in compliance with the Declaration of Helsinki and a written approval from the institution's ethics committee was obtained prior to the initiation of the study.

Patients attending the clinic were assessed with general physical examination, digital rectal examination (DRE), weight and height measurement, blood pressure measurement and uroflometry. Symptoms assessment was performed with IPSS. Blood test on serum PSA, fasting blood glucose, fasting cholesterol level and creatinine were done. Urine tests including mid-stream urine for culture and microscopy, as well we urine cytology, were offered. X-ray of kidney, ureter and bladder (KUB) was available to all patients. Transrectal ultrasound (TRUS)-guided prostate biopsy was carried out when there was suspicion of prostate cancer (abnormal DRE or PSA >4 ng/mL). Flexible cystoscopy and ultrasound or computer tomography (CT) of the urinary system were executed when patients were suspected of malignancy in the urinary tract.

Patients with the following features were excluded from the analysis: (a) patients diagnosed of urinary tract malignancy, (b) patients with history of prostate or bladder surgery, (c) patients with urethral stricture or bladder stone, (d) patients with history of ketamine abuse, (e) patients with previous radiotherapy to prostate or bladder.

Framingham risk score was developed under a project of the National Heart, Lung, and Blood Institute and Boston University, with an objective to identify the common factors that contribute to different kinds of heart diseases. The study was performed in the town of Framingham, Massachusetts, and the subjects were assessed every 2 years since 1948. From the Framingham Coronary Heart Disease Risk Score, age, gender, smoking status, cholesterol levels, blood pressure, and hypertensive treatments are considered the main factors to estimate the risk of coronary heart disease [8]. These factors, as well as fasting glucose and body mass index (BMI), were used to assess the presence of any correlation with LUTS.

SPSS version 21.0 was used for all analyses. P values <0.05 were considered statistically significant and 95% confidence interval (CI) was quoted along all analysis. Continuous variables were compared using Kruskal–Wallis test. Categorical variables were tested by Pearson Chi squared analysis. Multinomial logistic regressions were used to determine association between the predictors and the outcome. Furthermore, the regressions were adjusted by PSA level and the use of alpha-blockers. The correlations between cardiovascular risk and irritative symptoms were assessed by multiple linear regressions.

Results

From January 2013 to September 2015, 1176 patients were referred to our clinic for assessment. One-hundred and twenty-nine patients were excluded from the analysis as they were diagnosed of prostate cancer, bladder cancer or kidney cancer in the assessment. Other patients excluded from the analysis were: 30 patients had prostate or bladder surgery; 12 patients had urethral stricture or bladder stone; 2 patients had history of ketamine abuse; 37 patients had incomplete data. In the end, 966 subjects were included in the final analysis of the study.

The mean age of the cohort was 66.73 ± 10.17 years, with a mean total PSA 5.99 ± 6.33 ng/mL and a mean BMI of 24.18 ± 3.36 kg/m^2 (Table 1). As can be seen from the patient data in Table 1, 53% of our cohort had moderate LUTS, which was defined as an IPSS 8–19 points. Mild LUTS (IPSS ≤ 7) accounted for 22%, and severe LUTS (IPSS 20–35) accounted for the rest. Sixty percent of the patients had already been on alpha-blocker for the management of LUTS before they were referred to our clinic.

When we compared the features between different LUTS severity, Kruskal–Wallis tests showed that in all the independent variables, age ($P=0.001$) and Framingham risk score ($P=0.026$) increased as category of symptoms severity increased whereas PSA level ($P=0.02$) decreased with LUTS severity level (Table 2). In the Chi squared analyses, history of hypercholesterolaemia ($P=0.037$) and use of alpha-blockers ($P=0.002$) were significantly different between the three severity categories. On the other hand, BMI, blood pressure and smoking status did not show any difference in the three different LUTS severity groups.

Table 1 Demographics and characteristics of subjects

Variables	Value
Number of patients	966
Mean age (years) ± SD	66.73 ± 10.17
Mean total PSA (ng/mL) ± SD	5.99 ± 6.33
Mean BMI (kg/m^2) ± SD	24.18 ± 3.36
Mean fasting glucose (mmol/L) ± SD	5.71 ± 1.10
Mean total cholesterol (mmol/L) ± SD	4.75 ± 0.95
Mean HDL (mmol/L) ± SD	1.47 ± 0.41
Mean LDL (mmol/L) ± SD	2.72 ± 0.83
Mean triglycerides (mmol/L) ± SD	1.23 ± 0.64
Mean systolic BP (mmHg) ± SD	136.84 ± 20.57
Mean diastolic BP (mmHg) ± SD	80.85 ± 11.60
Mean Framingham risk score (%) ± SD	15.37 (8.16)
Mean total IPSS ± SD	14.11 ± 7.55
Mean storage domain score of IPSS ± SD	7.02 ± 3.73
Mean voiding domain score of IPSS ± SD	7.10 ± 5.31
LUTS severity, *n* (%)	
Mild	213 (22.0)
Moderate	512 (53.0)
Severe	241 (25.0)
Subjects with smoking habit, *n* (%)	135 (14.0)
Subjects with diabetes mellitus, *n* (%)	194 (20.1)
Subjects with hyperlipidaemia, *n* (%)	355 (36.7)
Subjects with hypertension, *n* (%)	511 (52.9)
Subjects with alpha-blockers, *n* (%)	579 (60.0)

LUTS severity Mild (IPSS ≤ 7); moderate (IPSS 8–19); severe (IPSS 20–35)

SD Standard deviation, *PSA* prostate-specific antigen, *BMI* body mass index, *HDL* high density lipoprotein cholesterol, *LDL* low density lipoprotein cholesterol, *BP* blood pressure, *IPSS* international prostate symptom score; *LUTS* lower urinary tract symptoms

In Table 3, LUTS severity and its correlation with cardiovascular risks were investigated. Upon multinomial logistic regression of LUTS severity, comparing moderate and severe LUTS against mild LUTS, Framingham risk score was found to be significantly correlated (likelihood ratio test Chi square 8.242, $P = 0.016$). When individual component in the algorithm of Framingham risk calculation was assessed individually, both age and blood cholesterol level were significantly associated with LUTS severity. Compared to patients with mild LUTS, patients with severe LUTS were more likely to be of a more advanced age (OR = 1.032 per year, 95% CI = 1.011–1.054), as well as with a higher total cholesterol level (OR = 1.318 per mmol/L, 95% CI = 1.069–1.626). In Table 3, we also considered other cardiovascular risk factors outside the Framingham risk algorithm, namely BMI and fasting glucose. It does not affect the finding that age and total cholesterol level were still being significantly associated with symptom severity. For fasting glucose, patients with severe LUTS were less likely to have a higher fasting blood glucose level (OR = 0.864 per mmol/L, 95% CI = 0.749, 0.997) compared to patients with mild LUTS.

As atherosclerosis leading to pelvis and bladder ischaemia is postulated to be one of the mechanisms leading to LUTS [9], we investigated that the relationship between storage symptoms and cardiovascular risk factors. Storage symptoms domain of IPSS (frequency, urgency, and nocturia) was assessed and possible correlation with cardiovascular risk factors was studied. After PSA level was adjusted, Framingham risk score was found to be significantly correlated with LUTS severity (CC = 0.083, 95% CI = 0.054, 0.112, $P < 0.0001$) (Table 4). Concerning the individual component of Framingham risk score, only age and total cholesterol were significantly associated with storage symptoms score. An increase in 1 year of age and 1 mmol/L of total cholesterol would increase storage symptom score by 0.083 (95% CI = 0.059, 0.108) and 0.287 (95% CI = 0.039, 0.536), respectively. A similar finding was again noted even after considering BMI and fasting glucose. On the other hand, Framingham risk score was not found to be correlated with the voiding symptoms domain of IPSS, which are incomplete emptying, intermittency, weak stream and straining to void (CC = −0.029; $P = 0.185$).

Discussion

Both LUTS and cardiovascular diseases are becoming more prevalent with advancing age [10]. When there is increasing evidence that erectile dysfunction can be an early manifestation of coronary artery disease [11], interest has been gaining momentum in the urology community to investigate if there is a similar association between LUTS and cardiovascular diseases. One of the theories to suggest such association was by Karatas et al. [12]. They speculated that LUTS in particular nocturia induces sleep disturbances. It would increase the sympathetic activity and, at the same time, deprive the subject of a normal nocturnal fall in blood pressure. This non-dipping blood pressure variation may be an insidious risk factor for cardiovascular diseases.

Concerning the association between LUTS and cardiovascular diseases, diverse results were observed in different clinical studies. Lightner et al. looked into the association between coronary heart disease and nocturia. Men < 60 years of age were not found to display such association [13]. Wehrberger et al. assessed the relationship of coronary vascular disease and LUTS in community-dwelling men [14]. Cross-sectional and longitudinal analyses were performed with a mean follow-up of 6.1 years. With the same definition of mild, moderate and severe LUTS as in our study, Wehrberger et al. revealed that men with severe LUTS were at increased risk for coronary vascular disease and stroke. The same observation was not found in the groups

Table 2 Comparison of different lower urinary tract symptoms severity

Variables	LUTS			*P*
	Mild	Moderate	Severe	
Number of patients (%)	213 (22.0)	512 (53.0)	241 (25.0)	
Mean (SD)				
Age (years)	64.65 (10.33)	67.07 (10.27)	67.82 (9.59)	0.001†
Framingham risk score (%)	14.20 (8.15)	15.62 (8.26)	15.89 (7.88)	0.026†
Hypercholesterolaemia, *n* (%)	63 (29.6)	203 (39.6)	89 (36.9)	0.037‡
Alpha-blockers, *n* (%)	100 (46.9)	306 (59.8)	173 (71.8)	0.002‡
Total PSA level (ng/mL)	6.49 (6.04)	6.00 (6.49)	5.54 (6.21)	0.020†
Body mass index (kg/m^2)	24.11 (3.74)	24.22 (3.36)	24.15 (3.00)	0.847†
Fasting glucose (mmol/L)	5.83 (1.27)	5.69 (1.03)	5.66 (1.07)	0.566†
Total cholesterol (mmol/L)	4.71 (0.96)	4.72 (0.95)	4.84 (0.95)	0.425†
HDL (mmol/L)	1.46 (0.36)	1.47 (0.41)	1.49 (0.45)	0.880†
LDL (mmol/L)	2.70 (0.86)	2.70 (0.82)	2.79 (0.84)	0.807†
Triglycerides (mmol/L)	1.25 (0.60)	1.21 (0.63)	1.24 (0.63)	0.679†
Systolic BP (mmHg)	138.21 (21.65)	136.62 (20.0)	136.10 (20.77)	0.283†
Diastolic BP (mmHg)	82.07 (11.90)	80.67 (11.69)	80.14 (11.09)	0.081†
Smoking habit, *n* (%)	33 (15.5)	74 (14.4)	28 (11.6)	0.445‡
Diabetes mellitus, *n* (%)	51 (23.9)	105 (20.5)	38 (15.8)	0.089‡
Hypertension, *n* (%)	108 (50.7)	216 (42.2)	127 (52.7)	0.732‡

LUTS Lower urinary tract symptoms, *SD* standard deviation, *PSA* prostate-specific antigen, *HDL* high density lipoprotein cholesterol, *LDL* low density lipoprotein cholesterol, *BP* blood pressure

†Kruskal–Wallis test

‡Chi square analysis

Table 3 Multinomial logistic regression of urinary symptoms severity level and cardiovascular risk factors

Predictors	Moderate LUTS		Severe LUTS	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Framingham risk score	1.027 (1.005, 1.049)	0.015	1.033 (1.009, 1.059)	0.008
The reference category is Mild LUTS. Adjusted by PSA				
Components of Framingham risk score				
Age	1.023 (1.006, 1.041)	0.057	1.032 (1.011, 1.054)	0.006
Smoking habit	0.925 (0.589, 1.452)	0.734	0.717 (0.412, 1.248)	0.239
Hypertension	0.921 (0.645, 1.313)	0.648	0.796 (0.526, 1.204)	0.279
Total cholesterol	1.105 (0.923, 1.324)	0.276	1.318 (1.069, 1.626)	0.010
The reference category is Mild LUTS. Adjusted by the use of alpha-blockers and PSA level				
Different cardiovascular risk factors				
Age	1.025 (1.007, 1.043)	0.006	1.034 (1.012, 1.056)	0.002
BMI	1.012 (0.963, 1.064)	0.625	1.011 (0.953, 1.071)	0.723
Smoking habit	0.903 (0.573, 1.421)	0.658	0.696 (0.399, 1.215)	0.203
Hypertension	0.961 (0.665, 1.387)	0.831	0.839 (0.546, 1.290)	0.425
Fasting glucose	0.864 (0.749, 0.997)	0.045	0.842 (0.705, 1.006)	0.058
Total cholesterol	1.085 (0.905, 1.301)	0.378	1.290 (1.044, 1.594)	0.018
The reference category is Mild LUTS. Adjusted by the use of alpha-blockers and PSA level				

LUTS severity Mild (IPSS ≤ 7); moderate (IPSS 8–19); severe (IPSS 20–35)

LUTS Lower urinary tract symptoms, *OR* odds ratio, *PSA* prostate-specific antigen, *BMI* body mass index

of mild and moderate LUTS. When analysing the data from a primary care setting database in The Netherlands, Bouwman et al. showed that men with LUTS were not more likely to develop cardiovascular diseases, at any time, than men without LUTS [15].

Table 4 Linear regression of storage symptoms score in IPSS and cardiovascular risk factors

Predictors	Coefficients (95% CI)	*P*
Framingham risk score	0.083 (0.054, 0.112)	< 0.0001
Adjusted by PSA level		
Components of Framingham risk score		
Age	0.083 (0.059, 0.108)	< 0.0001
Smoking habit	−0.219 (−0.873, 0.435)	0.511
Hypertension	0.016 (−0.479, 0.510)	0.950
Total cholesterol	0.287 (0.039, 0.536)	0.024
Adjusted by the use of alpha-blockers and PSA level		
Different cardiovascular risk factors		
Age	0.084 (0.060, 0.109)	< 0.0001
Body mass index	0.016 (−0.054, 0.085)	0.655
Smoking habit	−0.244 (−0.899, 0.412)	0.466
Hypertension	0.048 (−0.463, 0.559)	0.854
Fasting glucose	−0.146 (−0.359, 0.068)	0.181
Total cholesterol	0.271 (0.021, 0.085)	0.034
Adjusted by the use of alpha-blockers and PSA level		

PSA Prostate-specific antigen

When a causal relationship between LUTS and cardiovascular diseases cannot yet be demonstrated in the literature, effort has been cast to look into a possible link between LUTS and individual cardiovascular risk factor. Our study was an attempt to define such association. In our study, Framingham risk score was found to correlate with the severity of LUTS. Framingham risk score is based on an algorithm that estimates the absolute risk of atherosclerotic cardiovascular diseases in general. This general cardiovascular disease risk function also demonstrates a very good discrimination and calibration for predicting the risk of individual cardiovascular disease entity, which includes coronary heart disease, stroke, intermittent claudication and heart failure [8]. Such ability is due to these disease entities sharing a common set of risk factors, and such parallelism is based on an atherosclerosis-based pathogenesis. The pathogenesis of LUTS is considered to be multifactorial, and some hypotheses have been attributing LUTS to endothelial dysfunction and pelvic atherosclerosis [9]. In animal model, Azadzoi et al. showed that atherosclerosis-induced chronic ischaemia increases TGF-beta1 expression in the bladder, which in turn leads to fibrosis, smooth muscle atrophy and non-compliance [16]. The same animal study also found that hypercholesterolaemia interferes with bladder structure and compliance. Furthermore, ischaemia may lead to structural changes in the prostate, affecting outlet resistance [17]. McVary proposed that with atherosclerosis-induced pelvic ischaemia, the induced autonomic nervous system hyperactivity, and reduced NOS expression and the upregulation of Rho-kinase would in the end result in LUTS [9]. In light of this theory, it is reasonable to suggest that Framingham risk score correlates with LUTS and our study confirms such association. Furthermore, our data demonstrated that Framingham risk score correlates with storage symptoms but not voiding symptoms in IPSS. Considering atherosclerosis-induced ischaemia affects predominantly the bladder with deposition of collagen [18] and urothelial/suburothelial alterations [19], our finding is compatible with the pelvic ischaemia status. As a result, this reduction in blood flow, endothelial dysfunction and upregulation of free radicals appears to contribute to bladder overactivity.

In our analysis, age and cholesterol level correlated to the severity of LUTS. Age as a risk factor for LUTS has been observed in previous epidemiological research without being studied in the perspective of cardiovascular disease correlation [20]. The similarity of having age as a common risk factor is a reason to look into these two entities together. An animal study by Rahman et al. provides insights into the possible mechanism between hypercholesterolaemia and LUTS [21]. In their study, rats with hypercholesterolaemia developed significantly more bladder overactivity than the controls. Furthermore, hyercholesterolaemia rats were found to have more P2X1 receptors, which are important for normal contractions of the bladder, and more P2X3 receptors, which are implicated in bladder overactivity. These findings echo our result of cholesterol level correlating with LUTS.

Lim et al. reported their finding of risk factors for LUTS in a population of Malay, Chinese and Indian [22]. Overall, age, ethnicity, education, history of hypertension, diabetes, hypercholesterolaemia as well as prostate volume were found to be significantly associated with moderate-to-severe LUTS. Interestingly, different cardiovascular risk factors correlated with LUTS in different ethnicity. For Indian, history of diabetes and hypercholesterolaemia was strongly associated with

moderate-to-severe LUTS. On the other hand, only hypertension was found to be significantly related to the severity of LUTS in Chinese. Our cohort in the study was entirely of Chinese ethnicity. However, hypertension status was not noted to be relevant to LUTS in our study. The difference between our findings and that of Lim et al. could be due to a difference in hypertension duration and hypertension control between these two cohorts, thus possibly masking hypertension as a risk factor in our study. Further study is needed to verify the role of hypertension in LUTS.

A limitation of our study is the lack of an asymptomatic control group. Furthermore, this is a cross-sectional study which cannot imply any temporal causal relationship between the outcome and the predictors. The role of cardiovascular risk factors in LUTS would be more thoroughly investigated in a longitudinal setting with the involvement of asymptomatic population. However, considering the high prevalence of LUTS in our cohort with a mean age of 67 years old, the use of mild LUTS as a reference for analysis is a reasonable option. In addition, prostate volume was not available in our cohort for adjustment during regression analysis. As PSA level can predict prostate volume, our analyses used PSA level as a surrogate in an attempt to correct the bias introduced by prostate volume variation.

In conclusion, our present cross-sectional study highlighted the significant association between LUTS and cardiovascular risk factors as manifested by the Framingham risk score. Storage symptoms correlated to cardiovascular factors better than voiding symptoms, in particular age and total cholesterol level.

Authors contribution CHY: Protocol, project development, data collection, data analysis, manuscript writing. JSYY: Protocol, project development, data collection, data analysis, manuscript writing. NMYC: Project development, data collection. CHK: Project development, data collection. KML: Project development, data collection. JYCT: Project development, data collection. PKFC: Project development, data collection. JHMW: Project development, data collection. ESYC: Project development, data collection. CKC: Project development, data collection. SSMH: Project development, data collection. CFN: Project development, data collection.

Compliance with ethical standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and animal participants right All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

1. Yee CH, Li JK, Lam HC, Chan ES, Hou SS, Ng CF (2014) The prevalence of lower urinary tract symptoms in a Chinese population, and the correlation with uroflowmetry and disease perception. Int Urol Nephrol 46(4):703–710
2. De Nunzio C, Kramer G, Marberger M et al (2011) The controversial relationship between benign prostatic hyperplasia and prostate cancer: the role of inflammation. Eur Urol 60(1):106–117
3. Vignozzi L, Gacci M, Maggi M (2016) Lower urinary tract symptoms, benign prostatic hyperplasia and metabolic syndrome. Nat Rev Urol 13(2):108–119
4. Bouwman II, Blanker MH, Schouten BW et al (2015) Are lower urinary tract symptoms associated with cardiovascular disease in the Dutch general population? Results from the Krimpen study. World J Urol 33(5):669–676
5. Gacci M, Corona G, Sebastianelli A et al (2016) Male lower urinary tract symptoms and cardiovascular events: a systematic review and meta-analysis. Eur Urol 70(5):788–796
6. Bushman W (2009) Etiology, epidemiology, and natural history of benign prostatic hyperplasia. Urol Clin North Am 36(4):403–415
7. Balakumar P, Maung UK, Jagadeesh G (2016) Prevalence and prevention of cardiovascular disease and diabetes mellitus. Pharmacol Res 113(Pt A):600–609
8. D'Agostino RB Sr, Vasan RS, Pencina MJ et al (2008) General cardiovascular risk profile for use in primary care: the Framingham heart study. Circulation 117(6):743–753
9. McVary K (2006) Lower urinary tract symptoms and sexual dysfunction: epidemiology and pathophysiology. BJU Int 97(Suppl 2):23–28 **(discussion 44–5)**
10. Zakaria L, Anastasiadis AG, Shabsigh R (2001) Common conditions of the aging male: erectile dysfunction, benign prostatic hyperplasia, cardiovascular disease and depression. Int Urol Nephrol 33(2):283–292
11. Dong JY, Zhang YH, Qin LQ (2011) Erectile dysfunction and risk of cardiovascular disease: meta-analysis of prospective cohort studies. J Am Coll Cardiol 58(13):1378–1385
12. Karatas OF, Bayrak O, Cimentepe E, Unal D (2010) An insidious risk factor for cardiovascular disease: benign prostatic hyperplasia. Int J Cardiol 144(3):452
13. Lightner DJ, Krambeck AE, Jacobson DJ et al (2012) Nocturia is associated with an increased risk of coronary heart disease and death. BJU Int 110(6):848–853
14. Wehrberger C, Temml C, Gutjahr G et al (2011) Is there an association between lower urinary tract symptoms and cardiovascular risk in men? A cross sectional and longitudinal analysis. Urology 78(5):1063–1067
15. Bouwman II, Kollen BJ, van der Meer K, Nijman RJ, van der Heide WK (2014) Are lower urinary tract symptoms in men associated with cardiovascular diseases in a primary care population: a registry study. BMC Fam Pract 15:9
16. Azadzoi KM, Tarcan T, Siroky MB, Krane RJ (1999) Atherosclerosis-induced chronic ischemia causes bladder fibrosis and non-compliance in the rabbit. J Urol 161(5):1626–1635
17. Kozlowski R, Kershen RT, Siroky MB, Krane RJ, Azadzoi KM (2001) Chronic ischemia alters prostate structure and reactivity in rabbits. J Urol 165(3):1019–1026
18. Nomiya M, Burmeister DM, Sawada N et al (2013) Effect of melatonin on chronic bladder-ischaemia-associated changes in rat bladder function. BJU Int 112(2):E221–E230
19. Sunagawa M, Wolf-Johnston A, Nomiya M et al (2015) Urinary bladder mucosal responses to ischemia. World J Urol 33(2):275–280
20. Irwin DE, Milsom I, Hunskaar S et al (2006) Population-based survey of urinary incontinence, overactive bladder, and other

lower urinary tract symptoms in five countries: results of the EPIC study. Eur Urol 50(6):1306–1314 **(discussion 14–5)**
21. Rahman NU, Phonsombat S, Bochinski D, Carrion RE, Nunes L, Lue TF (2007) An animal model to study lower urinary tract symptoms and erectile dysfunction: the hyperlipidaemic rat. BJU Int 100(3):658–663
22. Lim J, Bhoo-Pathy N, Sothilingam S et al (2015) Cardiovascular risk factors and ethnicity are independent factors associated with lower urinary tract symptoms. PLoS One 10(6):e0130820