BJUI
BJU International

Functional Urology

Increase of Framingham cardiovascular disease risk score is associated with severity of lower urinary tract symptoms

Giorgio I. Russo, Tommaso Castelli, Salvatore Privitera, Eugenia Fragalà, Vincenzo Favilla, Giulio Reale, Daniele Urzì, Sandro La Vignera*, Rosita A. Condorelli*, Aldo E. Calogero*, Sebastiano Cimino and Giuseppe Morgia

*Department of Urology, and *Department of Medical and Paediatric Sciences, Section of Endocrinology, Andrology and Internal Medicine, University of Catania, Catania, Italy*

Objective

To determine the relationship between lower urinary tract symptoms (LUTS)/benign prostatic hyperplasia (BPH) and 10-year risk of cardiovascular disease (CVD) assessed by the Framingham CVD risk score in a cohort of patients without previous episodes of stroke and/or acute myocardial infarction.

Patients and Methods

From September 2010 to September 2014, 336 consecutive patients with BPH-related LUTS were prospectively enrolled. The general 10-year Framingham CVD risk score, expressed as percentage and assessing the risk of atherosclerotic CVD events, was calculated for each patient. Individuals with low risk had ≤10% CVD risk at 10 years, with intermediate risk 10–20% and with high risk ≥20%. Logistic regression analyses were used to identify variables for predicting a Framingham CVD risk score of ≥10% and moderate–severe LUTS (International Prostate Symptom Score [IPSS] ≥8), adjusted for confounding factors.

Results

As category of Framingham CVD risk score increased, we observed higher IPSS (18.0 vs 18.50 vs 19.0; $P < 0.05$), high IPSS–voiding (6.0 vs 9.0 vs 9.5; $P < 0.05$) and worse sexual function. Prostate volume significantly increased in those with intermediate- vs low-risk scores (54.5 vs 44.1 mL; $P < 0.05$). Multivariate logistic regression analysis showed that intermediate- [odds ratio (OR) 8.65; $P < 0.01$) and high-risk scores (OR 1.79; $P < 0.05$) were independently associated with moderate–severe LUTS. At age-adjusted logistic regression analysis, moderate–severe LUTS was independently associated with Framingham CVD risk score of ≥10% (OR 5.91; $P < 0.05$).

Conclusion

Our cross-sectional study in a cohort of patients with LUTS–BPH showed an increase of more than five-fold of having a Framingham CVD risk score of ≥10% in men with moderate–severe LUTS.

Keywords

LUTS, metabolic syndrome, prostate, cardiovascular disease, benign prostatic obstruction, Framingham score

Introduction

Recent studies have strengthened the hypothesis regarding the connection between LUTS secondary to clinical BPH, erectile dysfunction (ED) and cardiovascular disease (CVD). In fact, recent reports suggested that concomitant morbidities, e.g. diabetes, smoking, metabolic syndrome or hypercholesterolaemia, increased with ageing, leading to a greater severity of LUTS and reduction of sexual function [1–3]. More recently, results of large community-based studies were published on the association between CVD and LUTS [4] or CVD and nocturia [5].

However, besides these major premises, connections between LUTS and endothelial dysfunction are far from being understood [6], but proposed underlying mechanisms may be secondary to the alteration of the nitric oxide (NO)–cyclic guanosine monophosphate (cGMP) pathway [7], enhancement of RhoA–Rho-kinase (ROCK) signalling [8], autonomic hyperactivity [9] and pelvic atherosclerosis [10,11]. While all of these mechanisms are at least partly influenced by CVD risk factors, the last two are largely interrelated with hypertension, diabetes, metabolic syndrome and related conditions [12,13]. In fact, as the rate of CVD risk increases through classes, the severity of LUTS and ED also increase,

 | doi:10.1111/bju.13053
Published by John Wiley & Sons Ltd. www.bjui.org

suggesting that the contribution of atherosclerosis and autonomic hyperactivity could potentiate other mechanisms and impact disease severity [12].

However, several drawbacks are evident in the current literature that limit the correct interpretation of such association from an epidemiological point of view, such as the lack of standardisation of patients included, or consideration of multiple risk factors. Although studies have assessed associations between ED and future CVD events, as well as cross-sectional associations between Framingham CVD risk score and ED, no studies have assessed the link between LUTS and Framingham CVD risk.

The aim of the present cross-sectional study was to determine the relationship between LUTS–BPH and 10-year risk of CVD assessed by the Framingham CVD risk score in a cohort of patients without previous episodes of stroke and/or acute myocardial infarction (MI).

Patients and Methods

From September 2010 to September 2014, 328 consecutive patients with BPH-related LUTS were prospectively enrolled in this cross-sectional study at a single academic outpatient clinic. Patients with neurogenic bladder, post-void residual urine volume of >150 mL, prostate cancer, bladder cancer, bladder stone, urethral stricture, previous diagnosis of diabetes, previous episodes of CVD (stroke and/or acute MI) and hypogonadism (total testosterone [TT] level <8 nmol/L or serum testosterone in the range 8–11 nmol/L and free testosterone <220 pmol/L, assessed at least on two occasions) were excluded from the study. The Internal Institutional Review Board (Ethics Committee Approval No. 578/12) approved the protocol and an informed written consent was obtained from each patient before enrolment. The study was conducted in accordance with the regulatory standards of Good Clinical Practice and the Declaration of Helsinki (1996).

Patients underwent physical examination, including DRE and prostate volume estimated by TRUS. For each patient, detailed medical and sociodemographic data were collected. Blood samples were drawn from overnight-fasting patients and serum levels of PSA, fasting blood glucose, high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol and triglyceride were recorded. A venipuncture was performed between 08:00 and 10:00 hours for TT and oestradiol measurement. LUTS were evaluated by culturally and linguistically validated versions of the IPSS. LUTS severities were classified as mild (IPSS 0–7), moderate (IPSS 8–19) and severe (IPSS 20–35). The short form of the International Index of Erectile Function (IIEF) questionnaire was used for the assessment of patients' erectile function and the presence of ED was considered to be IIEF–erectile function <26 [14].

The general 10-year Framingham CVD risk score, expressed as a percentage, and assessing the risk of atherosclerotic CVD events (i.e. coronary heart disease, cerebrovascular disease, peripheral vascular disease and heart failure) was calculated for each patient, using age, HDL, total cholesterol level, systolic blood pressure, anti-hypertensive medication use, diabetes and current smoking status. Respectively, individuals with low risk had ≤10% CVD risk at 10 years, intermediate risk had 10–20% and high risk had ≥20%.

Statistical Analysis

All statistical analyses were completed using SPSS v. 19 software (SPSS Inc., IBM Corp., Somers, NY, USA). The continuous variables, presented as median (interquartile range, IQR), were tested by Mann–Whitney *U*-test or Kruskal–Wallis test, according to their non-normal distribution (normality of variables distribution was tested using the Kolmogorov–Smirnov test). Spearman's correlation coefficients were used to test the associations between the different variables. Linear regression models were performed for factors significantly correlated at

Table 1 Clinical characteristics of the patients.

Variables	Value
Number of patients	336
Median (IQR)	
Age, years	65.0 (58.0–72.0)
PSA level, ng/mL	3.67 (1.32–4.52)
TT, mg/dL	4.62 (3.37–5.82)
Prostate volume, mL	47.0 (34.0–60.0)
Body mass index, kg/m^2	26.83 (24.69–29.32)
Fasting glucose, mg/dL	92.0 (84.0–104.0)
Cholesterol, mg/dL	186.0 (160.0–220.0)
HDL, mg/dL	40.0 (34.0–49.0)
Systolic BP, mmHg	125.0 (120.0–140.0)
Diastolic BP, mmHg	80.0 (75.0–80.0)
IPSS	18.0 (13.0–22.0)
IPSS–storage	8.0 (5.0–11.0)
IPSS–voiding	9.0 (5.0–12.0)
LUTS, *n* (%)	
Mild	62 (18.5)
Moderate	154 (45.8)
Severe	120 (35.7)
Median (IQR)	
IIEF–erectile function	22.0 (16.0–25.0)
IIEF–orgasmic function	9.0 (8.0–10.0)
IIEF–sexual desire	8.0 (6.0–9.0)
IIEF–intercourse satisfaction	10.0 (7.0–11.0)
IIEF–overall satisfaction	8.0 (6.0–9.0)
ED (IIEF–erectile function <26), *n* (%)	236 (70.2)
Smoking habit, *n* (%)	90 (26.8)
Hypertension, *n* (%)	184 (54.8)
Median (IQR) Framingham CVD risk, %	16.0 (11.0–21.0)
Low Framingham CVD risk, *n* (%)	60 (17.9)
Intermediate Framingham CVD risk, *n* (%)	172 (51.2)
High Framingham CVD risk, *n* (%)	104 (31.0)

BP, blood pressure.

Spearman's analysis. Univariate and multivariate logistic regression analyses were carried out to identify variables for predicting Framingham CVD risk score of ≥10% and moderate–severe LUTS (IPSS ≥8), adjusted for confounding factors; 1 000 bootstrap resamples were used for all accuracy estimates and to reduce overfit bias. For all statistical comparisons a $P < 0.05$ was considered to indicate statistical significance.

Results

Table 1 lists the baseline characteristics of the patients. The median (IQR) age was 65.0 (58.0–72.0) years, IPSS was 18.0 (13.0–22.0) and Framingham CVD risk score was 16.0 (11.0–21.0). As category of Framingham CVD risk score increased, we observed higher IPSS (18.0 vs 18.50 vs 19.0; $P < 0.05$), higher IPSS–voiding (6.0 vs 9.0 vs 9.5; $P < 0.05$) and worse sexual function. Prostate volume significantly increased in intermediate- vs low-risk scores (54.5 vs 44.1 mL; $P < 0.05$). The proportion of Framingham CVD risk scores of ≥10% was 68.45% (230/336) in moderate–severe LUTS and 13.09% (44/336) in mild LUTS ($P < 0.05$) (Table 2).

Linear regression analysis showed a positive association between Framingham CVD risk score and IPSS (β = 0.16; $P < 0.01$; Fig. 1), IPSS–storage (β = 0.13; $P < 0.05$), IPSS–voiding (β = 0.14; $P < 0.01$) and IIEF–erectile function (β = −0.29; $P < 0.01$).

At age-adjusted logistic regression analysis, moderate–severe LUTS were independently associated with a Framingham CVD risk score of ≥10% (odds ratio [OR] 5.91, 95% CI 1.25–28.01; $P < 0.05$].

Similarly, multivariate logistic regression analysis showed that a Framingham CVD risk score of ≥10% (OR 4.85; $P < 0.05$) was independently associated with moderate–severe LUTS after adjusting for age, PSA level, body mass index and prostate volume. After adjusting for covariates, intermediate (OR 8.65; $P < 0.01$) and high (OR 1.79; $P < 0.05$) Framingham CVD risk scores were independently associated with moderate–severe LUTS (Table 3, Fig. 2). The bootstrapping calculations generally confirmed the P values of the conventional logistic regression analysis with larger ranges of 95% CI of the ORs.

Discussion

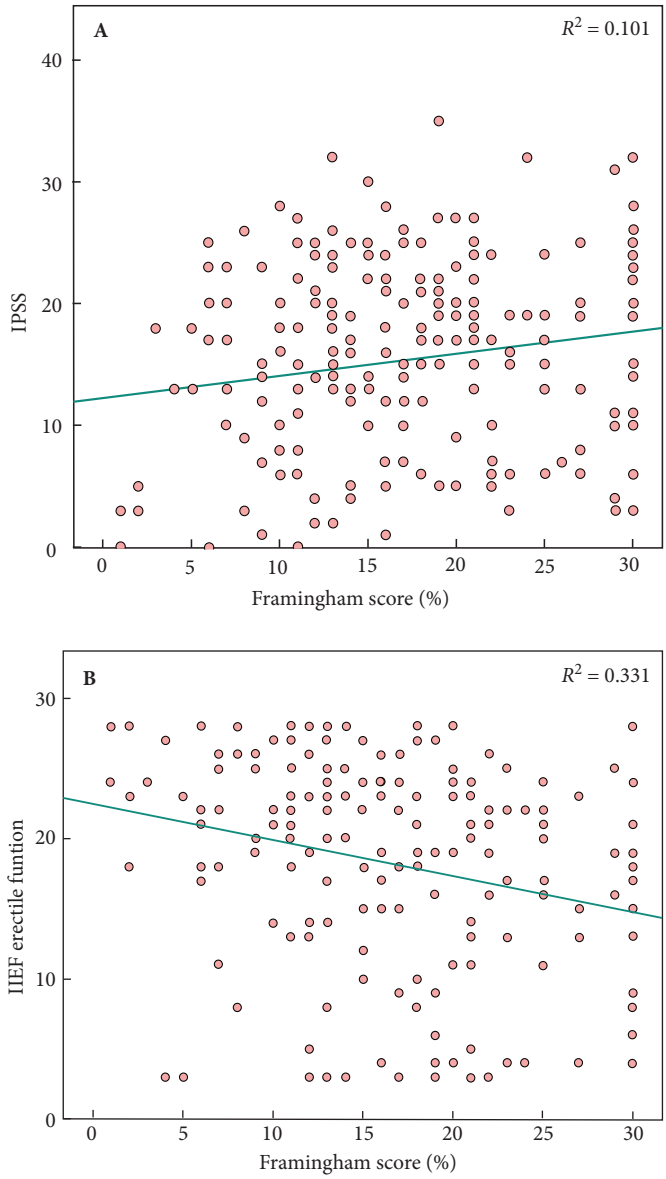
The findings of the present study evidenced the supposed close relationship between severity of LUTS and 10-year CVD

Table 2 Clinical characteristics of patients in each Framingham CVD risk score category.

Variables	Framingham CVD risk score category			*P*
	Low	Intermediate	High	
Number of patients	60	172	104	
Median (IQR)				
Age, years	54.0 (47.25–56.0)	65.0 (61.0–70.0)	73.0 (67.25–77.0)	<0.01*
PSA level, ng/mL	2.56 (1.18–4.60)	3.99 (3.0–4.5)	3.8 (1.29–4.8)	0.07*
TT, mg/dL	4.82 (2.97–4.96)	4.62 (3.55–6.07)	4.58 (3.45–5.72)	0.12*
Prostate volume, mL	44.1 (26.12–56.25)	54.5 (40.0–70.0)	43.5 (33.25–71.75)	<0.05*
Body mass index, kg/m^2	26.83 (24.66–28.48)	27.14 (25.25–29.38)	26.21 (24.55–27.74)	0.38*
Fasting glucose, mg/dL	89.0 (84.25–93.5)	95.0 (86.0–107.0)	92.0 (84.0–104)	<0.01*
Cholesterol, mg/dL	176.0 (154.0–202.5)	200.5 (169.0–229.0)	186.0 (162.0–203.5)	<0.01*
HDL, mg/dL	40.0 (37.5–42.75)	44.5 (34.0–54.0)	35.0 (31.25–43.0)	<0.01*
Systolic BP, mmHg	120.0 (120.0–127.5)	122.5 (120.0–130.0)	140.0 (130.0–162.25)	<0.01*
Diastolic BP, mmHg	80.0 (73.75–80.0)	80.0 (70.0–80.0)	80.0 (76.25–85.0)	0.09*
IPSS	18.0 (8.0–23.0)	18.5 (14.0–21.0)	19.0 (15.0–21.5)	<0.05*
IPSS–storage	8.0 (3.75–10.0)	7.5 (4.0–11.0)	8.0 (5.0–10.75)	0.47*
IPSS–voiding	6.0 (3.0–14.0)	9.0 (6.0–11.0)	9.5 (5.25–13.75)	0.05*
LUTS, *n* (%)				
Mild	16 (25.8)	28 (45.2)	18 (29.0)	0.31†
Moderate	26 (16.9)	76 (49.4)	52 (33.8)	
Severe	18 (15.0)	68 (56.7)	34 (28.3)	
Median (IQR)				
IIEF–erectile function	25.0 (20.25–28.0)	22.5 (18.0–25.0)	16.0 (11.0–22.0)	<0.01*
IIEF–orgasmic function	10.0 (8.75–10.0)	10.0 (8.0–10.0)	8.0 (4.5–9.0)	<0.01*
IIEF–sexual desire	8.0 (7.0–9.0)	8.0 (6.0–9.0)	7.0 (6.0–8.75)	<0.01*
IIEF–intercourse satisfaction	10.0 (8.0–11.5)	10.0 (8.0–11.0)	7.5 (3.0–10.75)	<0.01*
IIEF–overall satisfaction	8.0 (7.0–10.0)	8.0 (6.0–9.0)	6.0 (4.0–8.0)	<0.01*
ED (IIEF–erectile function <26), *n* (%)	36 (15.3)	114 (48.3)	86 (36.4)	<0.01†
Smoking habit, *n* (%)	8 (8.9)	40 (44.4)	42 (46.7)	<0.01†
Hypertension, *n* (%)	16 (8.7)	82 (44.6)	86 (46.7)	<0.01†
Median (IQR) Framingham CVD risk, %	6.0 (4.5–7.25)	14.0 (11.0–17.0)	25.0 (21.25–30.0)	<0.01*

**Kruskal–Wallis test. †Chi-squared analysis.*

Fig. 1 Age-adjusted linear regression analysis between Framingham CVD risk score and (**a**) IPSS and (**b**) IIEF–erectile function.



probability assessed by the Framingham CVD risk score. Although previous associations have been advanced about such interactions, the underlying hypotheses are still discussed. The pathogenesis of LUTS is considered to be multifactorial, in which age-related changes of bladder structure/function seem to play a central role [1]. Among all factors, endothelial dysfunction in the pelvic vascular system might contribute to bladder dysfunction, while increased sympathetic activity and/or α_1-adrenoreceptor activity might be a common pathway for both hypertension and LUTS [2]. Furthermore, diabetes mellitus can lead to increase severity of LUTS via neurogenic bladder dysfunction, with detrusor underactivity being the most common urodynamic pattern [4].

We have also recently shown that serum insulin increases were associated with greater severity of LUTS–BPH and ED [15]. It is plausible that insulin levels determine a lower synthesis and release of NO, owing to lower activity and expression of NO synthase, which is combined with an accelerated consumption of NO [16]. Therefore, when insulin resistance and disorders associated with glucose and lipid metabolism develop, there is a decrease in NO levels, leading to an alteration in the vasodilatation mechanisms mediated by the endothelium. This disruption in the normal endothelial vascular function, particularly in arterioles and capillaries, worsens the metabolic functions of insulin, producing a negative feedback mechanism.

In addition to age, LUTS and ED also share various other risk factors, e.g. obesity, high fasting plasma glucose levels, hypertension, androgen deficiency, depression and smoking, thus indicating that a metabolic syndrome might play a key role in the pathogenesis of both ED and severe LUTS [17].

It is likely that similar endothelial dysfunctions are also present in patients with CVD [18]. However, the causality between these connections and LUTS–BPH disease has not yet been determined.

Taking these premises into account, it should be noted that all previous pathogenetic mechanisms are known to increase CVD risk. In fact, such risk factors are currently evaluated, when calculating the Framingham CVD risk score, by including age, HDL, total cholesterol level, systolic blood pressure, anti-hypertensive medication use, diabetes and current smoking status [5].

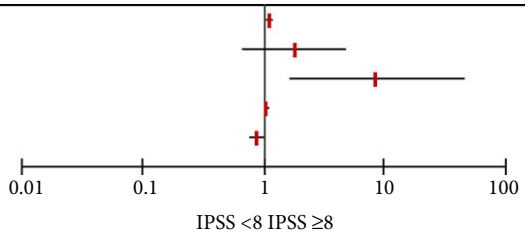
Table 3 Multivariate logistic regression analysis for significant predictors of moderate–severe LUTS (IPSS ≥ 8), adjusted for confounding factors.

Predictors	OR (95% CI)*	*P*	Predictors	OR (95% CI)*	*P*
Age, years	1.24 (1.14–1.35)	<0.01	Age, years	1.10 (1.04–1.16)	<0.01
TPV, mL	1.07 (1.03–1.10)	<0.01	TPV, mL	1.06 (1.04–1.08)	<0.01
TT, mg/dL	0.81 (0.70–0.96)	<0.05	TT, mg/dL	0.88 (0.78–0.99)	<0.05
Framingham CVD risk score ≥10%, yes vs no	4.85 (1.30–18.13)	<0.05	Low Framingham score	Ref. 1.00	<0.05
			Intermediate Framingham score	8.65 (1.65–45.35)	<0.01
			High Framingham score	1.79 (0.68–4.71)	0.24

*TPV, total prostate volume; Ref., reference; *Adjusted for body mass index.*

Fig. 2 ORs, as derived from a logistic regression model adjusted for age, PSA level, prostate volume, TT, body mass index and Framingham CVD risk score; SE, standard error; IV, Inverse Variance.

Study or subgroup	log[OR]	SE	OR IV, Fixed, 95% CI
Age (years)	0.0953	0.0286	1.10 [1.04, 1.16]
High Framingham score (%)	0.5822	0.4938	1.79 [0.68, 4.71]
Intermediate Framingham score (%)	2.1576	0.8453	8.65 [1.65, 45.35]
Total prostate volume (mL)	0.0583	0.0097	1.06 [1.04, 1.08]
Total testosterone (mg/dL)	−0.1278	0.0615	0.88 [0.78, 0.99]



Although Wehrberger et al [19]. recently showed that men with severe LUTS (IPSS ≥20) were at increased risk for CVD and stroke; they also reported that mild–moderate LUTS did not seem to be an age-independent risk factor for CVD and stroke. However, we think that these results could have been biased by the only 17 (0.8%) men affected by severe LUTS.

A recent cross-sectional analysis by Bouwman et al. [1], conducted on 1 610 men, reported an OR for CVD for men with moderate–severe LUTS of 1.81 (1.38–2.37, adjusted for age and other confounders). Interestingly, the study also included 1 248 CVD-free men in a longitudinal analysis, with a mean follow-up of 6.35 years. Multivariable Cox proportional regression analyses, with adjustment for age, obesity, hypertension, diabetes mellitus, current smoking and ED, yielded a hazard ratio of 1.08 ($P = 0.81$) for moderate–severe LUTS. We think that the small rate of men with moderate–severe LUTS (24.4%) and the lack of evaluation of Framingham CVD risk score in the same cohort could have influenced these negative results.

In this regard, statin medications are currently prescribed for both primary and secondary prevention of coronary heart disease, stroke and peripheral artery disease. Interestingly, their use was found to be associated with a 6.5–7 year delay in the new onset of moderate/severe LUTS or BPH in a population-based cohort study of 2 447 men [20].

Our present data reported an increased OR in men with moderate–severe LUTS for having a Framingham CVD risk score of ≥10% (OR 5.91; $P < 0.05$) at age-adjusted logistic regression analysis, and an increase risk of moderate–severe LUTS in men with intermediate (OR 8.65; $P < 0.01$) and high (OR 1.79; $P < 0.05$) Framingham CVD risk scores. Although we did not aim to define a direct link between LUTS–BPH occurrence and increased CVD risk, we may postulate common pathogenetic pathways between the two diseases. Although LUTS–BPH could not be related to MI, it may be a reliable risk evaluator of CVD risk, due to the affinity of risk factors.

To the best of our knowledge, this is the first study assessing the 10-year CVD risk, assessed by the calculation of the Framingham CVD risk score, in men with moderate–severe LUTS without previous episodes of stroke and/or acute MI. We have reported herein differences with respect to current literature, probably secondary to the distribution of severity of LUTS in our present cohort (81.5% with IPSS ≥8) and the calculation of long-term risk of CVD.

The present study has some limitations: first, the small sample size and lack of an age-matched control group; second, this study relied on a one-time measurement of CVD risk and metabolic assessment, which, because of large intra-individual variability, may have only a low ability to characterise a person's long-term CVD risk; third, LUTS–BPH variables were assessed simultaneously at baseline, therefore we did not observe an impact of metabolic serum levels or uroflowmetry parameters on risk of CVD events at a long-term follow-up. Furthermore, the lower rate of patients with mild LUTS (18.5%) and low Framingham CVD risk score (17.9%) could represent potential criticisms regarding evaluation of the connection between LUTS–BPH and CVD risk.

We suggest further investigation of this association in a longitudinal study of moderate–severe LUTS men in order to verify our present findings. Furthermore, we suggest that these patients should be carefully assessed for their CVD risk and that they should potentially be set preventive strategies.

In conclusion, our present cross-sectional study in a cohort of patients with LUTS–BPH showed an increase of more than five-fold of having a Framingham CVD risk score of ≥10% in men with moderate–severe LUTS. These findings should be considered during global medical assessment of patients and in establishing new preventive strategies.

Conflicts of Interest

None disclosed.

References

1 **Bouwman II, Blanker MH, Schouten BW et al.** Are lower urinary tract symptoms associated with cardiovascular disease in the Dutch general

population? Results from the Krimpen study. *World J Urol* 2014. [Epub ahead of print]. DOI: 10.1007/s00345-014-1398-y

2 **Kim S**, **Jeong JY**, **Choi YJ et al**. Association between lower urinary tract symptoms and vascular risk factors in aging men: the Hallym Aging Study. *Korean J Urol* 2010; 51: 477–82

3 **Russo GI**, **Cimino S**, **Fragala E et al**. Relationship between non-alcoholic fatty liver disease and benign prostatic hyperplasia/lower urinary tract symptoms: new insights from an Italian cross-sectional study. *World J Urol* 2014. [Epub ahead of print]. DOI: 10.1007/s00345-014-1392-4

4 **Ponholzer A**, **Temml C**, **Wehrberger C**, **Marszalek M**, **Madersbacher S**. The association between vascular risk factors and lower urinary tract symptoms in both sexes. *Eur Urol* 2006; 50: 581–6

5 **D'Agostino RB Sr**, **Vasan RS**, **Pencina MJ et al**. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008; 117: 743–53

6 **Brookes ST**, **Link CL**, **Donovan JL**, **McKinlay JB**. Relationship between lower urinary tract symptoms and erectile dysfunction: results from the Boston Area Community Health Survey. *J Urol* 2008; 179: 250–5

7 **Rosen RC**. Update on the relationship between sexual dysfunction and lower urinary tract symptoms/benign prostatic hyperplasia. *Curr Opin Urol* 2006; 16: 11–9

8 **McVary KT**. Erectile dysfunction and lower urinary tract symptoms secondary to BPH. *Eur Urol* 2005; 47: 838–45

9 **Lowe FC**. Treatment of lower urinary tract symptoms suggestive of benign prostatic hyperplasia: sexual function. *BJU Int* 2005; 95(Suppl. 4): 12–8

10 **Mouli S**, **McVary KT**. PDE5 inhibitors for LUTS. *Prostate Cancer Prostatic Dis* 2009; 12: 316–24

11 **Favilla V**, **Cimino S**, **Castelli T**, **Madonia M**, **Barbagallo I**, **Morgia G**. Relationship between lower urinary tract symptoms and serum levels of sex hormones in men with symptomatic benign prostatic hyperplasia. *BJU Int* 2010; 106: 1700–3

12 **Kirby M**, **Chapple C**, **Jackson G et al**. Erectile dysfunction and lower urinary tract symptoms: a consensus on the importance of co-diagnosis. *Int J Clin Pract* 2013; 67: 606–18

13 **Schouten BW**, **Bohnen AM**, **Bosch JL et al**. Erectile dysfunction prospectively associated with cardiovascular disease in the Dutch general population: results from the Krimpen Study. *Int J Impot Res* 2008; 20: 92–9

14 **Rosen RC**, **Riley A**, **Wagner G**, **Osterloh IH**, **Kirkpatrick J**, **Mishra A**. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* 1997; 49: 822–30

15 **Russo GI**, **Cimino S**, **Fragala E et al**. Insulin resistance is an independent predictor of severe lower urinary tract symptoms and of erectile dysfunction: results from a cross-sectional study. *J Sex Med* 2014; 11: 2074–82

16 **Cersosimo E**, **DeFronzo RA**. Insulin resistance and endothelial dysfunction: the road map to cardiovascular diseases. *Diabetes Metab Res Rev* 2006; 22: 423–36

17 **Fusco F**, **D'Anzeo G**, **Sessa A et al**. BPH/LUTS and ED: common pharmacological pathways for a common treatment. *J Sex Med* 2013; 10: 2382–93

18 **Karthikeyan VJ**, **Blann AD**, **Baghdadi S**, **Lane DA**, **Gareth Beevers D**, **Lip GY**. Endothelial dysfunction in hypertension in pregnancy: associations between circulating endothelial cells, circulating progenitor cells and plasma von Willebrand factor. *Clin Res Cardiol* 2011; 100: 531–7

19 **Wehrberger C**, **Temml C**, **Gutjahr G et al**. Is there an association between lower urinary tract symptoms and cardiovascular risk in men? A cross sectional and longitudinal analysis. *Urology* 2011; 78: 1063–7

20 **St Sauver JL**, **Jacobsen SJ**, **Jacobson DJ et al**. Statin use and decreased risk of benign prostatic enlargement and lower urinary tract symptoms. *BJU Int* 2011; 107: 443–50

Correspondence: Giorgio Ivan Russo, Department of Urology, School of Medicine Policlinico Hospital, University of Catania, Catania, Italy.

e-mail: giorgioivan@virgilio.it

Abbreviations: CVD cardiovascular disease; ED erectile dysfunction; HDL high-density lipoprotein; IIEF International Index of Erectile Function; IQR interquartile range; LDL low-density lipoprotein; MI myocardial infarction; NO nitric oxide; OR odds ratio; TT total testosterone.