Erectile Dysfunction Predicts Coronary Heart Disease in Type 2 Diabetes

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Objectives   We examined the predictive power of erectile dysfunction (ED) on coronary heart disease (CHD) events in Chinese men with type 2 diabetes.

Background   Subjects with diabetes are prone to develop cardiovascular complications. Erectile dysfunction is strongly associated with CHD in cross-sectional studies, but prospective data are lacking.

Methods   A consecutive cohort of men with no clinical evidence of cardiovascular disease underwent comprehensive assessments for diabetic complications. Erectile dysfunction was defined according to the definition of the National Institutes of Health Consensus Conference 1992. Coronary heart disease events were censored with centralized territory-wide hospital databases in 2005.

Results   Of 2,306 subjects (age: 54.2 ± 12.7 years; follow-up: 4.0 [range 1.7 to 7.1] years), 26.7% had ED at baseline. The incidence of CHD events was higher in men with ED than those without (19.7/1,000 person-years, 95% confidence interval [CI] 14.3 to 25.2 person-years vs. 9.5/1,000 person-years, 95% CI 7.4 to 11.7 person-years). Men who developed CHD events were older; had a higher frequency of ED and microvascular complications; had longer duration of diabetes; and had higher blood pressure, total cholesterol, low-density lipoprotein cholesterol, and urinary albumin/creatinine ratio but lower high-density lipoprotein cholesterol and estimated glomerular filtration rate than those without CHD events. Erectile dysfunction remained an independent predictor for CHD events (hazard ratio 1.58, 95% CI 1.08 to 2.30, p = 0.018) after adjustment for other covariates along with age, duration of disease, and use of antihypertensive agents and albuminuria.

Conclusions   In type 2 diabetic men without clinically overt cardiovascular disease, the presence of ED predicts a new onset of CHD events. Symptoms of ED should be independently sought to identify high-risk subjects for comprehensive cardiovascular assessments.   (J Am Coll Cardiol 2008;51:2045–50) © 2008 by the American College of Cardiology Foundation

Men with diabetes have a higher prevalence of erectile dysfunction (ED) compared with the general population. In these subjects, the prevalence of ED increases with age and duration and severity of disease (1,2). Studies in different populations have reported frequencies of ED ranging from 20% to 90%, depending on choice of assessment methods (3–6).

Recent studies suggest close associations between ED and atherosclerosis, and ED might serve as a clinical marker for coronary, peripheral, or cerebrovascular diseases (7–12). In cross-sectional studies, strong associations between calculated Framingham coronary risk score and ED have been reported (11,13,14). However, to date, the prognostic value of ED in predicting adverse cardiovascular events such as coronary heart disease (CHD) has not been confirmed in prospective analyses.

In the present study, we examined the impact of ED on the incidence of CHD events in a prospective cohort of Chinese type 2 diabetic men who did not have clinical evidence of cardiovascular diseases at baseline.

Abbreviations and Acronyms

ACEI = angiotensin-converting enzyme inhibitor

ACR = albumin/creatinine ratio

ARB = angiotensin receptor blocker

CHD = coronary heart disease

CI = confidence interval

DBP = diastolic blood pressure

ED = erectile dysfunction

eGFR = estimated glomerular filtration rate

IIEF = International Index of Erectile Function

PAD = peripheral arterial disease

SBP = systolic blood pressure

Methods

Patients and methods. Patients with diabetes were referred from general practitioners and general medical and specialist hospital clinics to the Prince of Wales Hospital Diabetes Centre for comprehensive assessment of complications and risk factors based on the European DIABCARE protocol (15). Between 1995 and 2005, 3,640 men were assessed. Patients with type 1 diabetes (n = 174) defined as acute presentation with diabetic ketoacidosis, heavy ketonuria (>3+), or continuous requirement of insulin within 1 year of diagnosis were excluded from this analysis. Patients with clinically evident cardiovascular diseases, including CHD, stroke, or peripheral arterial disease (PAD), at baseline were not included (n = 548). Information on ED by questionnaire was not available in 612 patients. Hence, 2,306 patients were included in the final analysis. Informed consent was obtained from all patients at the time of assessment to allow use of data for research purpose. The study was approved by the Chinese University of Hong Kong Clinical Research Ethics Committee.

Details of clinical assessments and laboratory assays were described previously (16). Presence of CHD-related events was defined as a past history of myocardial infarction, hospital admissions with heart failure, revascularization, or chest pain with abnormal electrocardiogram or stress test. Presence of stroke was defined as admission with typical neurological symptoms with or without recovery and confirmed on imaging. Peripheral arterial disease was defined as absent pedal pulses confirmed by ankle-brachial ratio ≤0.9 on Doppler ultrasound examination or a history of previous revascularization procedures. None of the patients in this consecutive cohort had a history of stroke, CHD, or PAD. For all study participants, the use of antihypertensive medications, lipid-lowering agents, and angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) at baseline was also recorded. Antihypertensive medications included all classes of drugs that are indicated for hypertension, other than ACEI/ARB. The use of lipid-lowering drugs included statins and fibrates.

Patients were asked directly whether they suffered from ED according to the definition of the National Institutes of Health (NIH) Consensus Conference 1992 (17). Erectile dysfunction was defined as the inability to attain and/or maintain penile erection sufficient for satisfactory sexual performance. The response to the question was either "Yes"

or "No." All patients had at least 2 urinary collections: a sterile, random spot urine sample was used to measure albumin/creatinine ratio (ACR) followed by a timed collection (4- or 24-h) for measurement of urinary albumin excretion rate. The definition of albuminuria was based on the mean value of ACR from both the timed and spot urinary samples. Normoalbuminuria was defined as a mean ACR ≤3.5 mg/mmol, microalbuminuria, 3.5 to 25 mg/mmol, and macroalbuminuria, ≥25 mg/mmol (18). Sensory neuropathy was defined as 2 of 3 abnormal signs or symptoms: numbness in lower limbs or reduced sensation with either monofilament or graduated tuning fork. Estimated glomerular filtration rate (eGFR; expressed in ml/min/1.73 m^2) was calculated with the abbreviated Modification of Diet in Renal Disease (MDRD) formula further adjusted for the Chinese ethnicity (19):

$$GFR = 186 \times \left[S_{CR} \times 0.011\right]^{-1.154} \times \left[age\right]^{-0.203} \times \left[0.742 \text{ if female}\right] \times \left[1.233 \text{ if Chinese}\right]$$

where S_{CR} is serum creatinine expressed as μmol/l and 1.233 is the adjusting coefficient for Chinese. Chronic kidney disease (CKD) was defined by eGFR <60 ml/min/1.73 m^2 (20).

Clinical outcomes. Hong Kong has a heavily subsidized health care system, and 95% of inpatient and chronic care are provided by public hospitals managed by the Hospital Authority. All clinical end points including hospital admissions and mortality were censored on July 30, 2005 with databases from the Hospital Authority Central Computer System, which records admissions to all public hospitals. These databases, including the Hong Kong Death Registry, were matched by a unique identification number, the Hong Kong Identity Card number, which is compulsory for all residents in Hong Kong and used by all government departments and major organizations. With the International Classification of Diseases-9th Revision code, hard CHD events were defined as: 1) acute myocardial infarction (code 410) or death due to coronary cause (code 410, 411 to 414, 428); or 2) other nonfatal CHD (code 411 to 414, procedure codes 36 and 00.66).

Statistical analysis. The analysis was performed with the Statistical Package for Social Sciences (version 11.5, SPSS Inc., Chicago, Illinois) package. Triglyceride and ACR were logarithmically transformed, owing to skewed distributions. All data are expressed as mean ± SD or median [interquartile range], as appropriate. The Student t test or analysis of variance was used for between-group comparisons for continuous variables, and the chi-square test was used for categorical variables. Logistic regression analysis was performed to identify factors associated with ED. Cox proportional hazards regression analysis was used to estimate the hazard ratio with 95% confidence interval (CI) for CHD events. Univariate analysis was performed with variables including ED; age; duration of diabetes; smoking history; use of antihypertensive, ACEI/ARB, or lipid-lowering

medications; glycosylated hemoglobin (HbA1c); fasting plasma glucose; baseline status of retinopathy, sensory neuropathy, and ACR; eGFR; body mass index; waist circumference; systolic blood pressure (SBP) and diastolic blood pressure (DBP); low-density lipoprotein cholesterol; high-density lipoprotein cholesterol; and triglycerides. Factors associated with CHD ($p < 0.1$) on univariate analysis were included in the multivariate analysis. A forward stepwise algorithm ($p < 0.10$ for entry, and $p < 0.05$ for stay) was used. A p value < 0.05 (2-tailed) was considered to be significant.

Results

In this cohort of 2,306 subjects (mean age 54.2 ± 12.7 years) with a median follow-up period of 4.0 years (interquartile range 1.7 to 7.1), 616 (26.7%) had ED according to the NIH definition. There was no difference in clinical and biochemical parameters between the 612 in whom information on ED was not available and the remainder (data not shown). Men with ED were older and had a longer duration of diabetes and higher SBP, high-density lipoprotein cholesterol, serum creatinine, and ACR but lower eGFR and body mass index than those without ED. They also had higher rates of retinopathy, sensory neuropathy, albuminuria, and chronic kidney disease and were more frequently using antihypertensive medications or lipid-lowering agents or taking ACEIs/ARBs (Table 1). After adjusting for other confounding factors on logistic regression modeling, ED at baseline was associated with age (odds ratio [95% CI] 1.03 [1.02 to 1.04], $p < 0.001$), body mass index (0.96 [0.93 to 0.99], $p = 0.007$), retinopathy (1.91 [1.52 to 2.39], $p < 0.001$), sensory neuropathy (1.65 [1.32 to 2.07], $p < 0.001$), use of antihypertensive medications (1.35 [1.07 to 1.71], $p = 0.013$), and use of ACEI/ARB (1.50 [1.16 to 1.93], $p = 0.002$).

Although there was no clinical evidence of cardiovascular disease at baseline, new CHD events occurred in 123 (5.3%) subjects during the 4-year observational period, giving an annualized incidence of 12.0/1,000 person-years (95% CI 9.90 to 14.1). In men with ED, the incidence was 19.7/1,000 person-years (95% CI 14.3 to 25.2) compared with 9.5 (95% CI 7.4 to 11.7) in those without ED. Men who developed new CHD events were older and had a longer duration of diabetes, higher SBP and DBP, total cholesterol, low-density lipoprotein cholesterol, and urinary ACR but lower high-density lipoprotein cholesterol and eGFR. These subjects also had higher frequencies of retinopathy, albuminuria, use of antihypertensive medications, and ED at baseline (Table 2).

On univariate Cox regression analysis, age (hazard ratio [95% CI] 1.04 [1.02 to 1.05], $p < 0.001$), duration of diabetes (1.06 [1.04 to 1.09], $p < 0.001$), SBP (1.02 [1.01 to 1.03], $p < 0.001$), albuminuria (3.42 [2.24 to 5.23], $p < 0.001$), retinopathy at baseline (2.38 [1.66 to 3.41], $p < 0.001$), eGFR (0.99 [0.98 to 0.99], $p < 0.001$), use of

| Table 1 | Clinical and Metabolic Characteristics of 2,306 Chinese Men With Type 2 Diabetes Stratified by the Presence of Erectile Dysfunction |

	Erectile Dysfunction		
	No	**Yes**	**p Value**
n (%)	1,690 (73.3)	616 (26.7)	
Age (yrs)	52.4 ± 13.0	59.0 ± 10.5	<0.001
Duration of diabetes (yrs)	5.3 ± 5.9	7.6 ± 6.5	<0.001
Waist (cm)	88.3 ± 9.7	87.9 ± 9.7	0.399
SBP (mm Hg)	132 ± 18	136 ± 20	<0.001
DBP (mm Hg)	78 ± 11	77 ± 11	0.450
Body mass index (kg/m^2)	25.2 ± 3.9	24.6 ± 3.7	0.001
HbA$_{1c}$ (%)	7.7 ± 1.9	7.9 ± 1.8	0.094
Fasting plasma glucose (mmol/l)	8.6 ± 3.3	8.9 ± 3.5	0.080
Total cholesterol (mmol/l)	5.2 ± 1.2	5.2 ± 1.2	0.645
HDL-cholesterol (mmol/l)	1.2 ± 0.3	1.3 ± 0.3	0.007
LDL-cholesterol (mmol/l)	3.2 ± 1.0	3.1 ± 0.9	0.254
Triglycerides (mmol/l), n (IQR)	1.35 (0.95–2.10)	1.32 (0.91–1.93)	0.252
Serum creatinine (μmol/l), n (IQR)	87 (76–100)	92 (81–110)	<0.001
Urine albumin/creatinine ratio (mg/mmol), n (IQR)	1.4 (0.6–6.1)	2.7 (0.7–18.0)	<0.001
eGFR (ml/min/1.73 m^2)	89.4 ± 25.4	79.1 ± 25.0	<0.001
Smoking (%)			0.020
Never-smoker	47.8	43.2	
Ex-smoker	26.6	32.4	
Current smoker	25.6	24.4	
Retinopathy (%)	19.2	38.5	<0.001
Sensory neuropathy (%)	19.8	36.7	<0.001
Albuminuria (%)			<0.001
Normoalbuminuria	68.1	53.9	
Microalbuminuria	21.0	25.1	
Macroalbuminuria	10.9	21.0	
Chronic kidney disease (%)	5.7	11.7	<0.001
Use of antihypertensive medications (%)	24.5	38.8	<0.001
Use of ACEI/ARB (%)	15.6	29.7	<0.001
Use of lipid-lowering agents	10.2	14.1	<0.01

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HbA$_{1c}$ = glycosylated hemoglobin; HDL = high-density lipoprotein; IQR = interquartile range; LDL = low-density lipoprotein; SBP = systolic blood pressure.

lipid-lowering agents (1.77 [1.01 to 3.11], $p = 0.047$), use of antihypertensive medications (2.34 [1.62 to 3.37], $p < 0.001$), use of ACEI/ARB (2.15 [1.40 to 3.30], $p < 0.001$), and ED (2.23 [1.55 to 3.20], $p < 0.001$) were associated with new CHD events. In addition, DBP (1.01 [1.00 to 1.03], $p = 0.09$) had borderline statistical significance. These factors were entered in a forward stepwise model for multivariate analysis to identify independent predictors. Erectile dysfunction remained an independent predictor of CHD events (hazard ratio 1.58 [95% CI 1.08 to 2.30], $p = 0.018$), after adjusting for other confounding factors. Other independent factors were age, duration of diabetes, use of antihypertensive medications, and baseline status of macroalbuminuria (Table 3). The Kaplan-Meier curves for CHD events in subjects stratified by ED separated early and continued to diverge over time ($p < 0.001$) (Fig. 1).

Table 2	Clinical and Metabolic Characteristics of 2,306 Chinese Men With Type 2 Diabetes Stratified by the Presence of New Onset of CHD Events		
	CHD Events		
	No	**Yes**	**p Value**
n (%)	2,184 (94.7)	123 (5.3)	
Age (yrs)	53.0 ± 12.8	58.5 ± 11.0	<0.001
Duration of diabetes (yrs)	5.8 ± 6.1	8.4 ± 6.4	<0.001
Waist (cm)	88.1 ± 9.8	89.0 ± 7.3	0.320
SBP (mm Hg)	133 ± 19	139 ± 19	<0.001
DBP (mm Hg)	77 ± 11	80 ± 10	0.004
Body mass index (kg/m^2)	25.0 ± 3.9	25.1 ± 3.2	0.701
HbA$_{1c}$ (%)	7.8 ± 1.9	7.9 ± 1.7	0.457
Fasting plasma glucose (mmol/l)	8.7 ± 3.4	9.1 ± 3.5	0.208
Total cholesterol (mmol/l)	5.2 ± 1.2	5.5 ± 1.3	0.002
HDL-cholesterol (mmol/l)	1.24 ± 0.34	1.17 ± 0.30	0.033
LDL-cholesterol (mmol/l)	3.2 ± 1.0	3.5 ± 1.0	<0.001
Triglycerides (mmol/l), n (IQR)	1.34 (0.93–2.05)	1.42 (1.01–2.09)	0.592
Serum creatinine (μmol/l), n (IQR)	88 (77–102)	93 (80–112)	0.005
Urine albumin/creatinine ratio (mg/mmol), n (IQR)	1.5 (0.6–7.7)	4.4 (1.1–48.1)	<0.001
eGFR (ml/min/1.73 m^2)	107.3 ± 31.6	98.5 ± 32.8	0.003
Smoking (%)			0.127
Nonsmoker	47.0	38.5	
Ex-smoker	28.1	29.5	
Current smoker	24.9	32.0	
Retinopathy (%)	23.3	40.2	<0.001
Erectile dysfunction (%)	26.0	39.3	0.001
Albuminuria (%)			<0.001
Normoalbuminuria	65.3	46.6	
Microalbuminuria	22.0	23.7	
Macroalbuminuria	12.7	29.7	
Chronic kidney disease (%)	7.1	10.7	0.144
Use of antihypertensive medications (%)	27.7	39.3	<0.01
Use of ACEI/ARB (%)	80.9	76.2	0.24
Use of lipid-lowering agents (%)	11.2	11.5	0.88

CHD = coronary heart disease; other abbreviations as in Table 1.

Table 3	Predictors of New Onset of CHD Events in 2,306 Chinese Men With Type 2 Diabetes With Multivariate Analysis		
	Hazard Ratio	**95% Confidence Intervals**	**p Value**
Age	1.02	1.00–1.04	0.026
Duration of diabetes	1.03	1.00–1.06	0.025
Albuminuria			
Normoalbuminuria	1.00		
Microalbuminuria	1.28	0.81–2.03	0.30
Macroalbuminuria	2.16	1.37–3.41	0.001
Use of antihypertensive medications	1.58	1.06–2.35	0.025
Erectile dysfunction	1.58	1.08–2.30	0.018

Other covariates not selected in the final model included SBP, DBP, retinopathy at baseline, eGFR, use of lipid-lowering agents, and use of ACEI/ARBs.
   Abbreviations as in Tables 1 and 2.

ported that 70% of patients with type 2 diabetes had ED. The association between ED and CHD might be due to their many common risk factors. The prevalence of ED was higher among subjects with diabetes and silent CHD (angiographically proven) than those with diabetes alone. In a cross-sectional study, the presence of ED was associated with a 14.8-fold increased risk of CHD and was the most efficient predictor among other conventional cardiovascular risk factors [8]. In another cross-sectional survey, 58% of type 2 diabetic men with angiographic evidence of CHD had symptoms of ED before the development of symptoms of angina [23]. These findings strongly support the notion that ED might be a surrogate marker for future CHD, although prospective data are lacking.

Approximately 25% of middle-age men are estimated, with the Framingham Risk Engine, to develop CHD within 12 years [12]. In the present study with a median follow-up period of 4.4 years, Chinese type 2 diabetic men with ED
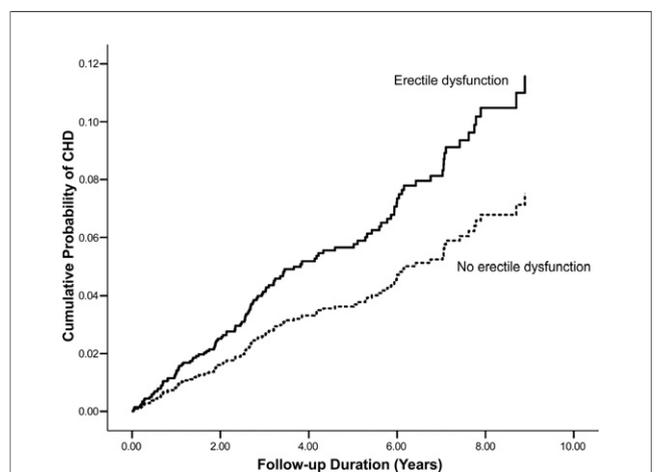
Discussion

In this cohort of Chinese men with type 2 diabetes and no clinical evidence of cardiovascular disease, 26% reported symptoms of ED. Erectile dysfunction was associated with age, disease duration, and presence of other microvascular complications. More importantly, men with ED had a 1.6-fold increased risk of developing CHD events than those without, after adjustment for age, duration of diabetes, and other cardiovascular risk factors.

Previous studies have documented that patients with diabetes are more likely to suffer from ED. In type 1 diabetes, symptoms of ED preceded typical symptoms of CHD by 38.8 months on average [21]. Although impotence—a manifestation of ED—is common in type 2 diabetes, most studies were retrospective or cross-sectional in nature. In a cross-sectional survey of type 2 diabetic patients, 34% reported problems of ED [22]. Giuliano et al. [1], with the International Index of Erectile Function (IIEF)-5 score, re-

Figure 1	Cumulative HR of CHD Events Stratified by ED in 2,306 Chinese Men With Type 2 Diabetes

Other covariates included age, duration of diabetes, systolic blood pressure, use of antihypertensive agents, low-density lipoprotein cholesterol, estimated glomerular filtration rate, retinopathy, and albuminuric status at baseline. CHD = coronary heart disease; ED = erectile dysfunction; HR = hazard ratio.

had an annualized CHD event rate of 20/1,000 person-years. This represents a 1.6-fold increased risk compared with those without ED. Compared with Caucasians, Chinese subjects are known to have lower risk of CHD (24). However, in this analysis, Chinese men with diabetes and ED had a CHD event rate comparable to the Caucasian general population (25). Importantly, the risk association between ED and new CHD events remained significant after adjustment for other confounding factors. Besides, none of these men had pre-existing cardiovascular diseases, thus strongly supporting that ED is an early marker of CHD in patients with diabetes. Recently, a guideline on identification of cardiovascular diseases in patients with diabetes was published (26). Our results argue that documentation of ED should be included in the assessment of cardiovascular risk.

Age, disease duration, and use of antihypertensive medications are important risk factors for CHD, in agreement with other reports (6,27–29). In addition, macroalbuminuria and ED conferred a 2- and 1.6-fold increased risk of CHD, respectively, independently of these risk factors. There are strong data showing that endothelial dysfunction is an important antecedent event in the development of CHD and atherosclerosis (30,31). There is consensus that albuminuria might be a marker of endothelial dysfunction (32). Although we did not measure endothelial dysfunction in these subjects, we have previously reported that Chinese type 2 diabetic patients with macroalbuminuria and renal dysfunction had reduced forearm flow-mediated dilation with Doppler ultrasound scan (33).

Taken together, it is conceivable that the penile micro-circulation might be affected early by metabolic and hemodynamic factors such as hyperglycemia, dyslipidemia, blood pressure, oxidative stress, and glycation end products. These might result in vascular dysfunction giving rise to ED characterized by delay in time to maximal erection, reduced rigidity, and decreased ability to sustain an erection. In these subjects, similar pathological processes might be expected in other parts of the circulation. Impaired endothelium-dependent and -independent vasodilation are present in diabetic patients with ED and precede the onset of overt CHD (34,35).

A potential limitation of the current study is the use of NIH criteria during interview to define ED. Sexuality is a cultural taboo in China. These factors might contribute to the relatively low frequency of ED as compared with other studies (1,2,36). In more recent studies, information on ED was collected by using the IIEF or IIEF-5 questionnaires, which include more objective items, rather than using a single question as in the NIH criteria. Nevertheless, the latter was regarded as the standard for assessment when the current study was initiated in 1995. Besides, other studies have indicated a reasonable correlation between subjective assessment by NIH criteria and more detailed assessment based on the IIEF-5 (1,37). Although this relatively low

percentage of subjects with ED is less likely to give rise to type 1 error, it is possible that subjects with more severe symptoms of ED were more likely to respond positively and thus bias the results toward a positive association. Nevertheless, in this prospective analysis, we have collected conventional risk factors and complications at baseline, and ED remained a significant risk factor after controlling for these confounding factors.

There are other limitations to this study. Selection bias might be present when patients are recruited from a single center. However, in Hong Kong, most patients with chronic diseases such as diabetes are managed in a public hospital where care is heavily subsidized. Although variability with single laboratory measurements might introduce errors, our results also demonstrate the benefit of asking a single question on ED and documenting clinical and biochemical measurement on a single occasion to identify subjects at high risk of CHD. When the survey was commenced in 1995, comprehensive cardiac assessments were not routinely performed in asymptomatic patients. Cardiovascular status was based largely on medical history or typical symptoms in the presence of abnormal electrocardiogram or stress test. Thus, it remains possible that patients with silent CHD might have been included in the analysis. Another potential limitation is the limited information on the use of concomitant medications, whereby effects from drugs such as beta-blockers or diuretics could not be separated from those due to other antihypertensive agents in terms of the relative contribution to ED in affected subjects. Although the use of antihypertensive medications was an independent predictor of new-onset coronary heart disease, impotence remains an independent predictor on Cox regression analysis. This finding suggested that the association between ED and new-onset CHD is unlikely to be accounted for by the influence of medications.

Conclusions

To our knowledge, this is the first prospective analysis of a large cohort of asymptomatic men with type 2 diabetes showing the risk association between ED and new onset of CHD events. These results strongly suggest that ED is a surrogate marker for future CHD. Given the preventable nature of CHD, symptoms of ED should be actively sought to identify high-risk subjects for comprehensive cardiovascular and metabolic assessments.

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