A cross-sectional observation to investigate subsequent cardiovascular diseases in Taiwanese men with erectile dysfunction

Chieh-Wen Chin¹, Bang-Ping Jiann¹,²

¹Department of Surgery, Division of Urology, Kaohsiung Veterans General Hospital, Kaohsiung, ²School of Medicine, National Yang-Ming University, Taipei, Taiwan

Abstract

Background: Erectile dysfunction (ED) is regarded as a warning of systemic disease. Controversy still exists in the relationship between ED and subsequent cardiovascular disease (CVD). This study aims to investigate the incidence and the interval of subsequent CVD in Taiwanese men who initially presented with the complaint of ED.

Materials and Methods: Consecutive ED patients without a history of obvious CVD at outpatient clinics from 1999 to 2013 were enrolled in the study. Data were collected by chart review and a structured interview through telephone calling. The main outcome measures were incidence and interval of subsequent CVD after the initial presentation of ED.

Results: During the study period, a total of 4713 patients presented at our clinics with the complaint of ED. After excluding patients who reported a history of major CVD (n = 347), younger than 40 years old (n = 484), and who did not have follow-up visit and could not be contacted (n = 409), 3473 patients’ data (73.7%) were found eligible for analysis. Their mean age was 62.2 ± 11.2 years (range: 40–91 years), and the mean follow-up period was 82.5 ± 51.8 months (range: 1–173 months). Of them, 9.1% (n = 316) had subsequent CVD with an ED–coronary artery disease temporal relationship of 58.7 ± 36.4 months (range: 1–170 months). Patients with subsequent CVD had a higher proportion of diabetes, hypertension (HT), and dyslipidemia compared with those who were free of subsequent CVD (P < 0.05). Age and comorbidities are independent risk factors for subsequent CVD in men with ED (P < 0.001). Of them, 7.4% (n = 258) expired, with malignancy (38.0%), infection (20.0%), and CVD (15.5%) being the three leading causes of death.

Conclusions: Among patients with ED, old age and having diabetes, HT, and dyslipidemia are associated with subsequent CVD. CVD risk reduction to halt the progress by lifestyle modification and well control of comorbidities should be advised to ED patients.

Keywords: Cardiovascular disease, comorbidities, erectile dysfunction, mortality

Access this article online

Quick Response Code:

Website: www.e-fjs.org

DOI: 10.4103/fjs.fjs_29_19

How to cite this article: Chin CW, Jiann BP. A cross-sectional observation to investigate subsequent cardiovascular diseases in Taiwanese men with erectile dysfunction. Formos J Surg 2020;53:1-7.
INTRODUCTION

Erectile dysfunction (ED) is a common medical disease and is defined as a recurrent or persistent inability for an individual to achieve and/or maintain penile erection sufficient for satisfactory sexual intercourse.[1] About one-fourth of Taiwanese men aged over 30 years reported having erectile problem as assessed by the Erection Hardness Scale.[2] ED is estimated to affect over 150 million men worldwide, with this number being expected to increase double by 2025.[3] Although it is considered a benign disease, ED affects not only quality of life but also men’s self-esteem and relationship with female partner.[4,5]

Cardiovascular disease (CVD) is the leading cause of death worldwide, accounting for 17.3 million deaths per year.[6] In Taiwan, CVD is the second-most common cause of mortality since 2010, imposing a great budgetary impact on the health-care system.[7] The prevalence of ED is high among CVD patients, including cerebrovascular accident (CVA), coronary artery disease (CAD), acute myocardial infarction (AMI), and peripheral arterial occlusive disease (PAOD).[8] Prospective studies indicate that ED is an earlier evidence of CVD.[9-11] Of patients with chronic CAD, 93% reported ED symptoms prior to the onset of angina pectoris, with a mean interval of 24 months.[12] Evidence demonstrate that CAD and ED overlap in risk factors, prevalence, and manifestation; they share both the etiology of and progression of the disease process.[10,13,14] Several pathological mechanisms were proposed to link between ED and CAD, including endothelium-derived nitric contractility, abundance and altered molecular regulation of smooth muscle contractility, autonomic neuropathy, androgens, and metabolic factors.[15]

Large population-based studies showed that ED is related to subsequent CVD.[8,14] Some studies reported that ED may not be a strong predictor but does increase risk to future cardiovascular (CV) events.[17,18] The presence of ED may provide an opportunity for CVD risk management in men without CVD.[19] The aim of the study was to investigate subsequent CVD prevalence and mortality causes in ED patients. We also analyzed the risk factors of subsequent CVD and the temporal relationship of ED–CVD.

MATERIALS AND METHODS

Study participants

A list of Taiwanese men diagnosed with ED and demographic data were retrieved from outpatient database at our institution from 1999 to 2013. Medical charts of all the participants were reviewed for the relevant information about CVD and the cause of mortality if there was. For participants with enough information through chart review, the last visit date was recorded as the end of follow-up for this study. Otherwise, a structured telephone interview would be attempted for all the participants by two registered nurses. The study protocol was reviewed and approved by the independent review board of our institution (IRB No. VGHKS12-CT12-01 obtained on Nov. 2nd, 2012). Written informed consent was not necessary for the participants.

Telephone interview

The study nurses received interview skills’ training first by the investigator. The interview would not be started until respondent’s identity was confirmed. After a brief introduction of the study, the nurse would declare a free willingness to answer the interview without any compensation. It usually took about 30 min to complete the interview. If the participant had been expired, cause of death would be obtained from his family instead. Participants who were unable to answer due to any reason or could not be reached by three callings at different times were categorized as lost to follow-up.

The structured questionnaire consisted of multiple-choice questions inquiring personal smoking habit, comorbidities, and ED medication history. If a history of subsequent CVD was present, type of disease and time of diagnosis would be inquired.

Outcome measures

The diagnosis of CVD was defined as having a history of angina, history of internal stent implantation for coronary artery, AMI, revascularization surgery, CVA, or PAOD by chart review or self-reporting during telephone interview. The ED–CVD temporal interval was derived from the time difference between the initial presentation for ED at our institution and the diagnosis of CVD. Presence of diabetes mellitus (DM), hypertension (HT), and dyslipidemia was retrieved from the chart review and confirmed again by telephone interview. CVD-caused mortality included CAD, CVA, peripheral vascular disease, heart failure, and other vascular diseases according to the International Classification of Diseases-10 code.[24]

Statistical analysis

The Chi-square test was used to compare categorical variables. Normality was assessed for continuous variables. The unpaired Student’s t-test or Mann–Whitney U-test was used to compare two continuous variables, depending on the normality of distribution. Data entry was performed using Excel 2000 (Microsoft, Redmond,
WA, USA). Statistical analyses were executed using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA). The null hypothesis was rejected for \( P > 0.05 \).

RESULTS

The study was conducted from 2014 to 2016. During a 14-year period from 1999 to 2013, a total of 4713 participants with a mean age of 59.0 ± 14.0 years (range: 20–91 years) complained of ED at our institution. Participants who reported a major CVD (347/4713 = 7.4%) at initial presentation for ED were older in age and had a higher prevalence of DM, HT, and dyslipidemia than participants who did not (4366/4713 = 92.6%) (all \( P < 0.001 \)). After excluding participants with age <0 years (\( n = 484 \)) and those who were lost to follow-up (unable to be contacted due to no telephone number and no follow-up visit) (\( n = 409 \)), 3473 (79.5%) participants’ data were eligible for the study [Figure 1]. Telephone calling had been attempted to 3473 participants, whereas 1475 (42.5%) had completed the interview, 637 (18.3%) refused to answer, and 1361 (39.2%) did not answer the phone in three callings.

Table 1 summarizes the 3473 participants’ demographic data and comorbidities. Their mean age was 62.2 ± 11.2 years (range: 40–91 years), and the mean follow-up interval from initial presentation to last visit or telephone interview was 82.5 ± 51.8 months (range: 1.0–173.0 months). HT (43.8%) was their most common comorbidity, followed by DM (27.6%) and dyslipidemia (22.0%). Of them, 9.1% of patients (\( n = 316 \)) developed subsequent CVD after initial presentation of ED, whereas CAD occurred in 53.2% (\( n = 168 \)), AMI in 10.8% (\( n = 34 \)), CVA in 31.6% (\( n = 100 \)), and PAOD in 4.4% (\( n = 14 \)) of patients, with a mean interval of 58.7 ± 36.4 months (range: 1–170 months). Table 2 summarizes the age and ED–CVD intervals between participants with and without subsequent CVD. Men with ED who developed subsequent CVD were older in age and had a higher proportion of DM, HT, and dyslipidemia when compared to those without subsequent CVD (all \( P < 0.01 \)). Post hoc analysis showed that the interval between the initial presentation of ED and the diagnosis of CVA was longer than that of CAD and PAOD (\( P = 0.017 \)) [Table 2]. Comparison of distribution by age groups in ED men who developed subsequent CVD with those who did not is shown in Table 3. The incidence of subsequent CVD increased with age (\( P < 0.001 \)). No statistically significant difference in ED–CVD interval existed among the age groups of ED by Breslow test (\( P = 0.168 \)) [Figure 2].

There were 258 (7.4%) deaths, and the leading causes of death are listed in Table 4. CVD-caused mortality ranked number three (15.5%), after malignancy (38.0%) and infection (20.0%).

Table 1: Demographic data and comorbidities of 3473 participants without a previous history of major cardiovascular disease at initial presentation of erectile dysfunction (\( n = 3473 \))

| Variables | Results |
|-----------|---------|
| Age, years | 62.2 ± 11.2 (40–91) |
| BMI, kg/m² | 24.6 ± 3.4 (13.8–41.4) |
| Follow-up period, months | 82.5 ± 51.8 (1–173) |
| Active or quit smoker, n (%) | 1033 (39.1) |
| Hypertension, n (%) | 1519 (43.8) |
| DM, n (%) | 959 (27.6) |
| Dyslipidemia, n (%) | 762 (22.0) |

DM: Diabetes mellitus, BMI: Body mass index

Figure 1: Flow diagram of the study participants. CVD: Cardiovascular disease, ED: Erectile dysfunction

Figure 2: The incidence of subsequent cardiovascular disease increased with age stratified by age groups
DISCUSSION

In this cross-sectional observational study, we aimed to investigate the incidence of subsequent CVD in 3473 men after their initial presentations for ED and their cause of mortality. Of them, 9.1% developed subsequent CVD, with a mean follow-up of 82.5 ± 51.8 months. The mean interval between the initial ED presentation and subsequent CVD is about 5 years. Patients with an older age, DM, HT, and dyslipidemia have an increased risk of subsequent CVD.

Of them, 7.4% expired, with malignancy, infection, and CVD being the three leading causes of death.

Erectile dysfunction increased the risk of subsequent erectile dysfunction

ED can be seen as a sentinel marker for subsequent CVD. In men with both ED and CVD, 67% (99/137) reported that ED symptoms were experienced before CVD symptoms for 39 months. Studies demonstrated that ED represents an independent risk factor for future CVD, even independent of conventional risk factors, namely DM and HT. In the Prostate Cancer Prevention Trial, men with ED had an increased risk of subsequent angina or myocardial infarction when compared with men without ED. In Chinese diabetic patients, relative risk of CVD event development for men with ED compared with those without ED was 1.6.

In addition to common risk factors, ED as a precursor of subsequent CVD can be based on similar pathophysiological mechanisms. Systemic endothelial dysfunction and inflammatory processes lead to atherosclerosis and ED. The artery size hypothesis has been proposed to address the ED onset before CVD events. Penile arteries are smaller in diameter (1–2 mm), whereas coronary arteries (3–4 mm) and internal carotid arteries (5–7 mm) are larger in diameter. The same level of plaque burden and endothelial dysfunction would have a greater effect on blood flow to the penile arteries than to the coronary, carotid, and femoral arteries because of the difference in artery size. Plaques would be an early sign in small-artery disease like ED which may occur in advance of CAD, AMI, or stroke.

Men with ED had a significantly higher incidence of atherosclerotic CV event. Younger age at first...
manifestation of ED, cigarette smoking, presence of comorbidities, and socioeconomic disadvantage are all associated with increased risks for subsequent atherosclerotic CV events. In the present study, DM, HT, and dyslipidemia were independent risk factors to subsequent CVD, whereas active or former cigarette smoking status had no association with it. Aging is thought to be a risk factor for developing CVD due to vascular endothelial dysfunction. In this study, the incidence of subsequent CVD increased from 2% to 4% with the increase of 10 years in age group.

Erectile dysfunction–coronary artery disease temporal relationship
The time interval between the CVD and ED presentation is about 5 years in this study. The result is correlated to a cross-sectional study, which revealed that ED may precede a CV event by as much as 5 years. Thompson et al. found that 5 years after the initial report of ED, 11% of the men had experienced an initial CV event. Montorsi et al. revealed that the time interval between ED and later CAD is 2–3 years. A cohort study found that 76.0% of subsequent atherosclerotic CV events had occurred within 15 years of the manifestation of ED. The median time interval was 11.9 years. In the COBRA trial, the severity of ED is related to different extents of CAD. Whether the severity of ED has influence on future CVD remains unclear and needs more investigation.

Erectile dysfunction and mortality
In this study, there were 258 deaths (7.4%), with CVD accounting for 15.5% of them. Our findings are consistent with that of another cohort study, including 1436 Chinese men in Hong Kong, in which CV mortality rate was about 10% in ED patients. The study also reported that ED was related not only with CV mortality but also with all-cause mortality. In a meta-analysis study, ED tended to increase the risk of CV death and predicted all-cause mortality. Due to improvement on medication and intervention procedures, CVD will not strictly contribute to CV death. In our study, CV mortality ranked the 3rd cause of death in ED patients, after malignancy and infection or pneumonia.

Malignancy has been the first major cause of death in Taiwan since 1994. High percentage of men consumed alcohol, betel nut, and cigarettes, resulting in a higher prevalence and mortality of oral cancer in Taiwan than elsewhere in the world. Taiwan also the highest prevalence of Hepatitis B virus infection in the world that is associated with cirrhosis and hepatocellular carcinoma. The link between those contributing factors to malignancy with ED patients is not known, but CVD remains one of the leading causes of death for ED patients in Taiwan.

Clinical implications
In the present study, almost 90% of patients had ED symptoms prior to CAD symptoms. ED plays an important role as a low-cost, noninvasive biomarker for systemic atherosclerotic disease. Given that ED is a predictor for subsequent CVD and taking into account the time interval between them, diagnosis of ED provides a golden opportunity for CVD risk reduction. All men with ED should receive a thorough medical assessment; biochemical determination of testosterone, fasting lipids, and fasting glucose levels; and prostate health examination. Early lifestyle and behavioral modifications, such as healthy diet, increasing physical activity, weight management, and smoking cessation, do lower CVD risk. On the other hand, improvement in CV risk factors also have benefits on patients’ erectile function.

Limitations
There are several limitations of this study. The diagnosis of comorbidities and CVD relied on self-report which probably over- or underestimated their incidences. The association of ED severity with the incidence of subsequent CVD was not known. We did not adjust the history of taking phosphodiesterase-V (PDE5) inhibitors in the study. Evidences supported a protective role of PDE5 inhibitor in patients for CVD. The timing of participant’s initial visit for ED was taken as the onset of ED. There is a latency time between the onset of ED and treatment seeking. Therefore, the real interval between ED and subsequent CVD should be longer than that in our study.

CONCLUSIONS
ED patients with an old age and having comorbidities are more likely to develop subsequent CVD than those who are younger and without comorbidities. Lifestyle modification as well as CV risk reduction should be offered to ED patients to reduce the comorbidity and improve general health.

Financial support and sponsorship
This investigator-initiated research was sponsored by Pfizer Inc. WI176209 (IIR 2013-03).

Conflicts of interest
There are no conflicts of interest.
in clinical practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention and Rehabilitation (EACPR). Eur Heart J 2016;37:2315-81.

37. Kriegsman DM, Penninx BW, van Eijk JT, Boeke AJ, Deeg DJ. Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly. A study on the accuracy of patients’ self-reports and on determinants of inaccuracy. J Clin Epidemiol 1996;49:1407-17.

38. Gandaglia G, Briganti A, Jackson G, Klomer RA, Montorsi F, Montorsi P, et al. A systematic review of the association between erectile dysfunction and cardiovascular disease. Eur Urol 2014;65:968-78.