Prediction of Coronary Artery Disease by Erectile Function Status: Evidence-Based Data

Graham Jackson, FRCP, FESC, FACC

Guy's and St Thomas' Hospitals NHS Trust, London, UK

DOI: 10.1002/smrj.12

ABSTRACT

The link between erectile dysfunction (ED) and cardiovascular disease (CVD) has been established as a result of individual studies and meta-analyses. ED predicts CVD, coronary disease, myocardial infarction, heart failure, and increased mortality. ED may occur on average 2–5 years before a CVD event and act as a marker for early asymptomatic vascular, and especially coronary artery, disease. Seventy percent of men with known CVD also have ED that identifies a further increased CVD event risk when compared with men with normal erections. Importantly, those at highest risk are men with ED aged 30–60 years and diabetics where CVD detection and prevention need the most focus. A question on ED should be incorporated in all CVD risk calculators, and when risk is identified, action to reduce risk should be aggressively initiated and monitored. **Jackson G. Prediction of coronary artery disease by erectile function status: Evidence-based data. Sex Med Rev 2013;1:104–107.**

Key Words. Erectile Dysfunction; Coronary Artery Disease; Risk; Assessment

Introduction

The link between erectile dysfunction (ED) and cardiovascular disease (CVD), especially coronary artery disease (CAD), has been the focus of many publications since it was first proposed in 2001 [1,2]. What has become clear over time is that ED may precede a cardiovascular event by an average of 3 years (range 2–5 years) [3,4]. In other words, ED is acting as a marker for subclinical vascular disease that is therefore asymptomatic [5]. Lesions in the coronary arteries of <50% stenosis do not usually influence flow but may be lipid rich with a thin fibrous cap and therefore vulnerable to rupture. Abrupt rupture could lead to a sudden occlusion (30% lesion progressing to 100%) and an acute coronary syndrome (ACS) including myocardial infarction (MI) or even death. Given that 60% of presentations with ACS or sudden death occur without warning, it is possible that ED could act as a "sentinel" for these acute and potentially devastating events [4].

Similarly, men with known CVD/CAD have an at least 70% incidence of ED that in turn is associated with further cardiovascular events and increased mortality compared with men who have normal erectile function [6]. Thus, the presence of ED is in the majority an indication of vascular pathology in general with endothelial dysfunction the common pathophysiological denominator [7].

ED and CVD: Examining the Link

The endothelium is the same throughout the arterial tree so it follows that if there is a problem at one part of the circulation (ED), there could be a problem elsewhere that need not be symptomatic (e.g., "silent" CAD or carotid disease). The artery size hypothesis seeks to explain the differing presentations of the same pathology and why ED could be a marker for silent disease elsewhere.

Artery size varies according to location within the vascular system (Table 1). For example, the lumen of the penile arteries is considerably smaller (1–2 mm) compared with that of the coronary (3–4 mm), carotid (5–6 mm), and femoral (6–8 mm) arteries. Because of their smaller size and greater surface area, the same level of plaque burden and/or endothelial dysfunction has a greater effect on blood flow through the penile arteries than through the coronary, carotid, and femoral arteries. Therefore, the clinical manifes-

Table 1 Artery size and atherothrombosis

Artery	Diameter (mm)	Clinical event
Penile	1–2	ED
Coronary	3–4	Ischemic heart disease
Carotid	5–7	TIA/stroke
Femoral	6–8	Claudication

A significant restriction to flow in the penile arteries may be subclinical in larger vessels.
ED = erectile dysfunction; TIA = transient ischemic attack

tations of penile endothelial dysfunction may become evident before the consequences of coronary or peripheral vascular disease. By the time the lumen of the larger arteries become significantly obstructed (>50%), the penile blood flow may have already decreased considerably, which explains why so many men with CAD have ED.

Thus, on the basis of the artery size hypothesis, a malfunction in the penile arteries causing ED may be a predictor of silent subclinical CVD. In addition, because an ACS often arises as a result of the rupture of a subclinical plaque, the presence of ED may also be an early warning sign of an acute coronary event including mortality.

In support of this concept, a series of 300 patients with acute chest pain and angiographically proven CAD were evaluated with a semistructured interview to assess their medical and sexual histories prior to presentation [8]. The prevalence of ED among these patients was 49% (n = 147). In these 147 men with both ED and CAD, ED was experienced before CAD symptoms in 99 patients (67%). The mean time interval between the occurrence of ED and the occurrence of CAD was 38.8 months (range 1–168 months). Interestingly, all men with ED and type I diabetes developed sexual dysfunction before the onset of CAD symptoms.

ED is more frequent in diabetic patients with silent CAD than in those without. In a study of men with type II diabetes (n = 260), the incidence of ED (International Index of Erectile Function [IIEF] questionnaire) was significantly higher in the population with asymptomatic CAD than in the population without CAD (33.8% vs. 4.7%; $P < 0001$) [9]. ED not only predicted CAD independently of other risk factors but also was the strongest predictor of silent CAD in this study.

The large Prostate Cancer Prevention Trial provided the first evidence of a strong association between ED and the subsequent development of clinical cardiovascular events [10]. ED at entry or that developed during follow-up was found to predict significantly any cardiac event with a hazard ratio of 1.45 ($P < 0.001$; 95% confidence interval 1.25–1.69). The data also showed that the cardiovascular risk associated with incident ED (that is developed during follow-up) was at least as great as the risk associated with a family history of MI, current smoking, or hypercholesterolemia.

The Temporal Relationship

Several studies suggest that there is a strong temporal relationship between ED and CAD, with ED preceding a cardiovascular event by at least 2–5 years. This temporal relationship was investigated in a questionnaire-based study that included 207 patients with CVD-attending cardiovascular rehabilitation programs and 165 age-matched controls from general practice in the United Kingdom [11]. Patients completed up to four questionnaires including the IIEF. Of the individuals with CVD, 56% were experiencing symptoms of ED at the time of the study and had done so for a mean of 5 ± 5.3 years. In contrast, 37% of individuals in the control group had ED symptoms for a mean of 6.6 ± 6.8 years. This interesting finding in the controls reflects the importance of asking about ED routinely.

In the Association between Erectile Dysfunction and Coronary Artery Disease trial, 93% of patients with a chronic coronary syndrome reported ED symptoms before the onset of angina pectoris, with a mean interval of 24 (range 12–36) months [12]. This finding further reinforces the concept of a lead time of at least 2–5 years between the development of ED and symptomatic CAD. The time intervals (range) for patients with one-, two-, and three-vessel disease were 12 (9.5–24), 24 (16.5–36), and 33 (21–47) months, respectively. There was a significant relationship between the length of time from ED to CAD onset and the number of vessels involved ($P = 0.016$). Importantly, given that men with ED may be at cardiovascular risk, this long lead time provides an early opportunity for cardiovascular risk reduction [13].

Prediction of CVD Events and Mortality

Two recent meta-analyses have greatly helped our assessment of the link between ED and the prediction of CVD and mortality [14,15]. Prior to these analyses three studies had evaluated the effect of age on the ED link to increased cardiovascular risk, identifying the importance of ED as an especially powerful predictor of CVD events in young and middle-aged men (ages 30–60 years) where CVD preventative resources should be maximized.

Table 2 ED predicts coronary events [16]

Age group 1,400 men with no known CAD—10-year follow-up	ED at baseline CAD events per 1,000 patient years with CI intervals	No baseline ED CAD events per 1,000 patient years with CI intervals
40–49	**48.52 (1.23–269.26)**	**0.94 (0.02–5.21)**
50–59	27.15 (7.40–69.56)	5.09 (3.38–7.38)
60–69	23.97 (11.49–44.10)	10.72 (7.62–14.66)
70+	29.63 (19.37–43.75)	23.30 (17.18–30.89)

Bold text illustrates major effect of age and is discussed in the text below. CAD = coronary artery disease; CI = confidence interval; ED = erectile dysfunction

A study of 1,400 men aged 40–75 years with no known CAD were prospectively followed for 10 years [16]. As can be seen from Table 2, men in their 40s with ED have a 50-fold increase in CAD events per 1,000 patient years compared with men with normal erectile function, and fivefold in men in their 50s. In a retrospective study from Western Australia over 10–15 years, men in their 20s and 30s were more than seven times more likely to have a CVD event if they had ED [17], and Riedner and colleagues found in a coronary angiographic study that CAD was 2.3 times higher in men <60 years of age with ED [18]. In all three studies, the ED/CAD link became less marked with age over 70 years.

Dong et al. performed a meta-analysis from 12 prospective studies involving 36,744 men [14]. In Table 3, the relative risks for men with ED are seen to be significantly increased for CVD, CAD, stroke, and all-cause mortality. Importantly, the ED risk was independent of conventional risk factors, and the mortality increase fits in with the rupture of a vulnerable plaque, as previously discussed.

Vlachopoulos and colleagues (Table 4) included 14 studies involving 92,757 men with similar findings to the Dong meta-analysis [15]. However, of especial importance is that they found the relative risk to be higher in younger men and intermediate risk groups (5–20% 10-year conventional risk).

Both meta-analyses confirmed that the presence of ED increases the risk for future CVD events,

Table 3 Relative risks for men with ED vs. no ED—first analysis [14]

		95% confidence interval	*P*
Overall relative risks	1.48	1.25–1.74	<0.001
CAD	1.46	1.31–1.63	<0.001
Stroke	1.35	1.19–1.54	<0.001
All-cause mortality	1.19	1.05–1.34	0.005

CAD = coronary artery disease; ED = erectile dysfunction

Table 4 Relative risks for men with ED vs. no ED—second analysis [15]

		95% confidence interval	*P*
Overall relative risks	1.44	1.27–1.63	<0.001
CAD (MI)	1.62	1.34–1.96	<0.001
Stroke	1.39	1.23–1.57	<0.001
All-cause mortality	1.25	1.12–1.39	<0.001

CAD = coronary artery disease; ED = erectile dysfunction; MI = myocardial infarction

MI, stroke, and all-cause mortality. ED should therefore be incorporated into routine clinical practice as a diagnosis needing treatment as well as a diagnosis that could trigger an aggressive CVD risk reduction strategy.

Conclusion

ED should be included in every CVD risk calculator. It costs nothing to ask the ED question—it is time to translate what we know into therapeutic action.

Corresponding Author: Graham Jackson, FRCP, FESC, FACC, Suite 301 Emblem House, London Bridge Hospital, 27 Tooley Street, London SE1 2PR, UK. Tel: 44-20-7407-5887; Fax: 44-20-7357-7408; E-mail: gjcardiol@talk21.com

Conflicts of Interest: None.

Statement of Authorship

Category 1

(a) Conception and Design
Graham Jackson

(b) Acquisition of Data
Graham Jackson

(c) Analysis and Interpretation of Data
Graham Jackson

Category 2

(a) Drafting the Article
Graham Jackson

(b) Revising It for Intellectual Content
Graham Jackson

Category 3

(a) Final Approval of the Completed Article
Graham Jackson

References

1 O'Kane PD, Jackson G. Erectile dysfunction: Is there silent obstructive coronary artery disease? Int J Clin Pract 2001;55:219–20.

2 Kirby M, Jackson G, Betteridge J, Friedli K. Is erectile dysfunction a marker for cardiovascular disease? Int J Clin Pract 2001;55:614–8.
3 Jackson G, Boon N, Eardley I, Kirby M, Dean J, Hackett G, Montorsi P, Montorsi F, Vlachopoulos C, Kloner R, Sharlip I, Miner M. Erectile dysfunction and coronary artery disease prediction: Evidence-based guidance and consensus. Int J Clin Pract 2010;64:848–57.
4 Nehra A, Jackson G, Miner M, Billups KL, Burnett AL, Buvat J, Carson CC, Cunningham GR, Ganz P, Goldstein I, Guay AT, Hackett G, Kloner RA, Kostis J, Montorsi P, Ramsey M, Rosen R, Sadovsky R, Seftel AD, Shabsigh R, Vlachopoulos C, Wu FC. The Princeton III Consensus recommendations for the management of erectile dysfunction and cardiovascular disease. Mayo Clin Proc 2012;87:766–78.
5 Jackson G, Padley S. Erectile dysfunction and silent coronary artery disease: Abnormal computed tomography coronary angiogram in the presence of normal exercise ECGs. Int J Clin Pract 2008;62:973–6.
6 Bohm M, Baumhakel M, Teo K, Sleight P, Probstfield J, Gao P, Mann JF, Diaz R, Dagenais GR, Jennings GL, Liu L, Jansky P, Yusuf S. Erectile dysfunction predicts cardiovascular events in high-risk patients receiving telmisartan, ramipril, or both: The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial/Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (ONTARGET/TRANSCEND) Trials. Circulation 2010; 121:1439–46.
7 Solomon H, Man JW, Jackson G. Erectile dysfunction and the cardiovascular patient: Endothelial dysfunction is the common denominator. Heart 2003;89:251–3.
8 Montorsi F, Briganti A, Salonia A, Rigatti P, Margonato A, Macchi A, Galli S, Ravagnani PM, Montorsi P. Erectile dysfunction prevalence, time of onset and association with risk factors in 300 consecutive patients with acute chest pain and angiographically documented coronary artery disease. Eur Urol 2003;44:360–4; discussion 64–5.
9 Gazzaruso C, Solerte SB, Pujia A, Coppola A, Vezzoli M, Salvucci F, Valenti C, Giustina A, Garzaniti A. Erectile dysfunction as a predictor of cardiovascular events and death in diabetic patients with angiographically proven asymptomatic coronary artery disease: A potential protective role for statins and 5-phosphodiesterase inhibitors. J Am Coll Cardiol 2008; 51:2040–4.
10 Thompson IM, Tangen CM, Goodman PJ, Probstfield JL, Moinpour CM, Coltman CA. Erectile dysfunction and subsequent cardiovascular disease. JAMA 2005;294:2996–3002.
11 Hodges LD, Kirby M, Solanki J, O'Donnell J, Brodie DA. The temporal relationship between erectile dysfunction and cardiovascular disease. Int J Clin Pract 2007;61:2019–25.
12 Montorsi P, Ravagnani PM, Galli S, Rotatori F, Veglia F, Briganti A, Salonia A, Deho F, Rigatti P, Montorsi F, Fiorentini C. Association between erectile dysfunction and coronary artery disease. Role of coronary clinical presentation and extent of coronary vessels involvement: The COBRA trial. Eur Heart J 2006;27:2632–9.
13 Jackson G. The importance of risk factor reduction in erectile dysfunction. Curr Urol Rep 2007;8:463–6.
14 Dong JY, Zhang YH, Qin LQ. Erectile dysfunction and risk of cardiovascular disease: Meta-analysis of prospective cohort studies. J Am Coll Cardiol 2011;58:1378–85.
15 Vlachopoulos CV, Terentes-Printzios DG, Ioakeimidis NK, Aznaouridis KA, Stefanadis CI. Prediction of cardiovascular events and all-cause mortality with erectile dysfunction: A systematic review and meta-analysis of cohort studies. Circ Cardiovasc Qual Outcomes 2013;6:1–11.
16 Inman BA, Sauver JL, Jacobson DJ, McGree ME, Nehra A, Lieber MM, Roger VL, Jacobsen SJ. A population-based, longitudinal study of erectile dysfunction and future coronary artery disease. Mayo Clin Proc 2009;84:108–13.
17 Chew KK, Finn J, Stuckey B, Gibson N, Sanfilippo F, Bremner A, Thompson P, Hobbs M, Jamrozik K. Erectile dysfunction as a predictor for subsequent atherosclerotic cardiovascular events: Findings from a linked-data study. J Sex Med 2010;7:192–202.
18 Riedner CE, Rhoden EL, Fuchs SC, Wainstein MV, Goncalves SC, Wainstein RV, Zago A, Bourscheit F, Katz N, Zago AJ, Ribeiro JP, Fuchs FD. Erectile dysfunction and coronary artery disease: An association of higher risk in younger men. J Sex Med 2011;8:1445–53.