

Erectile dysfunction

Cardiovascular disease and endothelial dysfunction



Bill Alexander,
Consultant
Physician
Western General
Hospital, Edinburgh

Topical issues in erectile dysfunction (ED) continue to focus on cardiovascular disease and endothelial cell dysfunction in men with and without diabetes. Endothelial dysfunction results in the inability of smooth muscle cells lining the arterioles to

relax, thus preventing vasodilatation; this endothelial response is significantly reduced in men with diabetes and ED. A damaged endothelium causes not only ED, but also atherosclerosis and cardiovascular disease.

Many clinical studies in men presenting solely with ED have revealed the presence of multiple cardiovascular risk factors, and often overt and severe coronary artery disease. Erectile function may indeed correlate with the severity of the underlying cardiovascular disease. This association should lead to the need for cardiology departments to become involved in the management of ED.

This need has led to a specialist nurse joining Dr Graham Jackson's team in the Department of Cardiology at St Thomas' Hospital, London; two

papers are presented from his department. The first usefully outlines the Princeton guidelines, a consensus previously mentioned in these pages. These guidelines address the management of ED in men with established cardiovascular disease, and stratify their cardiovascular status as low, intermediate or high risk. They are useful in the management of cardiovascular disease, as well as ED. (As a side issue, it may be wise to use short-acting PDE5 inhibitors in men in the high/intermediate-risk categories, and the long-acting tadalafil only in men in the low-risk category. Such advice may change as the role of phosphodiesterase type 5 (PDE5) inhibitors in the treatment of cardiovascular disease develops.) The second article looks at the detection of cardiovascular risk factors in men presenting with ED.

Other papers address hypertension and antihypertensive drugs, the use of a topical alprostadil cream, the efficacy of prostheses, the role of psychological factors and the impact of ED on quality of life. Finally, the paper by Sasaki et al on diabetes and urology provides a short review of diabetic cystopathy, which should be of interest to diabetes care professionals.

HEART



Endothelial dysfunction links ED and heart disease

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓✓✓✓

1 This article focuses on the relation between the cardiovascular patient and ED, and outlines management strategies for treating ED in the cardiovascular patient.

2 ED is highly correlated with vascular diseases such as hypertension, heart disease and diabetes, and may even be a marker for occult cardiovascular disease.

3 ED and vascular disease are thought to be linked at the level of the endothelium. Endothelial dysfunction results in an inability of the smooth muscle cells lining the arterioles to relax, thus preventing vasodilatation.

4 Increasing awareness of this association should encourage men to discuss their ED with medical practitioners.

5 The Princeton Consensus Guidelines have addressed the issue of the management of ED in men with established cardiovascular disease.

6 Cardiovascular risk stratification is the mainstay of these guidelines, enabling the identification of intermediate/high-risk patients who may continue to have uncontrolled cardiovascular disease.

7 Cardiovascular disease control must take priority over ED management in these patients.

8 In patients considered to have a low cardiovascular risk, the management of ED can be safe and effective.

Solomon H, Man JW, Jackson G (2003) Erectile dysfunction and the cardiovascular patient: endothelial dysfunction is the common denominator. *Heart* **89**: 251-4

INTERNATIONAL JOURNAL OF CLINICAL PRACTICE



Expanding role for cardiologists in the management of ED

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓✓✓✓

1 This study assessed the level of occult cardiovascular risk in men with ED, and evaluated the need for a cardiologist to be involved in the management of ED.

2 A total of 174 men presenting with ED underwent cardiac risk stratification according to the Princeton Consensus Guidelines: 30% were stratified as intermediate/high cardiovascular risk and had ED treatment deferred until further

cardiological assessment; 37% had abnormal lipid profiles; 24% had elevated HbA_{1c}/glucose levels; 17% had uncontrolled hypertension; and 6% were suspected of having significant angina.

3 This study demonstrates the high incidence of occult cardiovascular disease in men with ED, and supports the suggestion that ED is a marker for cardiovascular disease.

4 Through the presentation of ED, cardiac risk factors can be managed aggressively at an early stage, thereby reducing subsequent cardiac risk, morbidity and even possibly mortality.

5 A collaborative approach to the management of ED is recommended, with an expanding role for the cardiologist.

Solomon H, Man J, Wierzbicki AS, O'Brien T, Jackson G (2003) Erectile dysfunction: cardiovascular risk and the role of the cardiologist. *International Journal of Clinical Practice* **57**(2): 96-9

‘Data suggest that ED in patients with diabetes and hypertension may be related more to the higher age and prevalence of macrovascular disease, than to hypertension or its treatment.’

‘These two phase-2 studies showed that, in a population demonstrating a broad range of ED intensity, topical alprostadil was both effective and well tolerated.’



DIABETIC MEDICINE

ED related to hypertension and drug therapy

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

- ED is common in diabetes and may be related to the high prevalence of hypertension and consequent antihypertensive drug therapy in patients with diabetes.
- The risk factors for ED were studied with particular reference to hypertension and antihypertensive drugs.
- A retrospective case-note analysis was performed on 763 consecutive male patients (34% type 1

diabetes, 65% type 2 diabetes) attending an adult diabetes clinic to collect data on risk factors for ED. The use of anti-hypertensive drugs was specifically recorded.

4 Of the men reviewed, 299 (39%) had ED. The mean age of patients with ED (61 years) was higher than those without (51 years, $P<0.001$). The mean age of hypertensive patients was also significantly higher than those without hypertension.

5 On multivariate regression analysis, age ($P<0.001$), macrovascular disease ($P<0.001$), sensorimotor neuropathy ($P<0.001$) and HbA_{1c} ($P<0.05$) predicted ED. Neither hypertension nor any anti-hypertensive medication independently predicted ED.

6 Regarding the antihypertensive medications, erectile problems were more common among patients on angiotensin-converting enzyme

inhibitors, calcium-channel blockers and thiazide diuretics, but not among those on β -blockers or α -blockers.

7 Not surprisingly, increasing age emerged as the strongest independent predictor of ED. A sharp rise in prevalence of erectile problems was noted between the fifth decade (27%) and sixth decades (50%).

8 Erectile problems were more common among smokers compared with non-smokers and ex-smokers, although smoking did not independently predict ED.

9 Data suggest that ED in patients with diabetes and hypertension may be related more to the higher age and prevalence of macrovascular disease, than to hypertension or its treatment.

Moulik PK, Hardy KJ (2003) Hypertension, anti-hypertensive drug therapy and erectile dysfunction in diabetes. *Diabetic Medicine* 20: 290–3



INTERNATIONAL JOURNAL OF IMPOTENCE RESEARCH

Topical alprostadil cream treats ED in phase-2 studies

Readability	✓✓
Applicability to practice	✓✓
WOW! factor	✓✓✓

1 The most commonly used drug for local ED therapy is alprostadil, the synthetic formulation of prostaglandin E₁. Alprostadil produces corpora cavernosal smooth muscle relaxation predominantly by the activation of adenylate cyclase and the subsequent accumulation of 3,5-cAMP. This mechanism is independent of the nitric oxide-cGMP mechanism and does not require sexual stimulation.

2 Topical application of alprostadil has to date been explored in phase-1 and in-office studies with modest results.

3 This article presents the first at-home phase-2 examination of the efficacy and safety of a topical application of alprostadil cream in doses of 0, 0.05, 0.1, 0.2 and 0.3 mg in combination with a novel, proprietary permeation-enhancing agent for the treatment of mild-to-moderate and severe ED.

4 In two multicentre, placebo-controlled studies, patients with mild-to-moderate ($n=161$, study 1) or severe ($n=142$, study 2) ED were randomised to receive placebo, 0.05, 0.1 or 0.2 mg (study 1) or placebo, 0.1, 0.2 or 0.3 mg (study 2) of topically applied alprostadil (containing a proprietary skin permeation enhancer). The primary efficacy endpoint in both studies was the change in erectile function score from baseline to final visit.

5 The changes from baseline for erectile function scores were -0.8 ± 1.1 , 1.8 ± 1.1 , 0.7 ± 1.2 and 3.7 ± 1.2 ($P<0.01$, study 1) and 2.7 ± 1.3 , 6.29 ± 1.4 , 6.49 ± 1.5 and 9.44 ± 1.5 ($P<0.001$, study 2) for ascending dose groups in each study.

6 In both studies, the primary efficacy endpoint (change in erectile function domain score relative to baseline) was significantly increased in the highest dose treatment group, and dose-related trends in efficacy for all treatment groups were seen.

7 Topical alprostadil in this study was well tolerated, with the most common local adverse event being urogenital pain. This adverse event was dose-related and was primarily localised to the application site. Most of these adverse events (>97%) were of mild or moderate intensity, and of short duration.

8 These two phase-2 studies showed that, in a population demonstrating a broad range of ED intensity, topical alprostadil was both effective and well tolerated. These studies support the rationale for phase-3 studies, which are currently ongoing.

Padma-Nathan H, Steidle C, Salem S, Tayse N, Yeager J, Harning R (2003) The efficacy and safety of a topical alprostadil cream, Alprox-TD[®], for the treatment of erectile dysfunction: two phase-2 studies in mild-to-moderate and severe ED. *International Journal of Impotence Research* 15: 10–17

‘Penile prosthesis implantation continues to be an important option for men with ED. Overall, penile prostheses are believed to result in the highest satisfaction for the patient and partner, largely owing to reliability and ease of use.’



Penile prostheses improve erectile function

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓

1 Penile prosthetic surgery is associated with high satisfaction rates for patients. However, studies have failed to use instruments that accurately record patient satisfaction.

2 In this study, two validated instruments were used to assess the chronology of efficacy and satisfaction profiles in men undergoing penile prosthetic surgery.

3 Men who elected penile implant surgery were administered the International Index of Erectile Function (IIEF) questionnaire preoperatively, and 3, 6 and 12 months postoperatively, as well as the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) questionnaire 3, 6 and 12 months postoperatively.

4 Preoperative and postoperative values for the overall IIEF, IIEF erectile function domain, IIEF satisfaction domain and EDITS were compared. All surgeries were primary, and an inflatable implant device was placed in all patients.

5 A total of 96 men, with a mean age of 56 years, were enrolled in the study. All 12-month scores were statistically significantly higher than baseline scores. The 12-month values were statistically higher than 6-month values for the IIEF satisfaction domain and for EDITS.

6 In the analysis using the satisfaction domain of the IIEF questionnaire and the EDITS questionnaire, satisfaction scores were significantly higher at 12 months compared with baseline. Furthermore, IIEF satisfaction domain and EDITS scores at 12 months were significantly higher than at 6 months, suggesting that continued satisfaction was achieved as patients passed into the second half of postoperative year one.

7 Penile prosthesis implantation continues to be an important option for men with ED. Overall, penile prostheses are believed to result in the highest satisfaction for the patient and partner, largely owing to reliability and ease of use.

Mulhall JP, Ahmed A, Branch J, Parker M (2003) Serial assessment of efficacy and satisfaction profiles following penile prosthesis surgery. *Journal of Urology* **169**: 1429–33

‘This article underlines the interplay of clinical and psychological factors for determining the risk of ED in type 2 diabetes, and can help to identify patients in whom much greater attention is needed to detect erectile problems.’



Clinical and psychological factors in ED risk

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓

1 This article estimated the prevalence of self-reported ED, and identified subgroups of patients in which the interaction among clinical, psychological and sociodemographic characteristics caused a substantial increase in the likelihood of ED.

2 Clinical information was obtained from patients using ad-hoc study forms. For all clinical variables, the last value in the previous 12 months was requested. Patients are scheduled to be followed-up for 5 years, with information collected at 6-month intervals. This article reported a cross-sectional evaluation based on baseline patient data.

3 All patients were asked to complete a structured, anonymous questionnaire on how often the patient had had problems attaining and maintaining erection in the past 6 months. The study protocol did not include any clinical or instrumental diagnostic procedures.

4 Depressive symptoms were investigated using the Centre for Epidemiological Studies Depression (CES-D) Scale. This widely used, self-reported depression measure is composed of 20 items addressing symptoms of depression during the previous 4 weeks.

5 To evaluate interactions among the variables investigated and identify distinct, homogeneous subgroups of patients with different odds ratios (OR) for ED, a ‘tree-growing’ technique was used.

6 In the 1460 patients studied, the prevalence of severe ED was 34%, and mild–moderate ED was 24%. While severe ED was mainly related to the severity of diabetes, mild–moderate dysfunction was independent of clinical variables and only associated with the severity of depressive symptoms.

7 The ‘tree-growing’ technique led to the identification of six classes characterised by a marked difference in the prevalence of severe ED of between 19–65%. Patients on diet alone showed the lowest prevalence of ED and were considered the reference category, while patients treated with insulin who had neuropathy represented the subgroup with the highest likelihood of ED (OR=7.2, 95% confidence interval (CI)=3.9–13.2). In patients treated with oral agents, the OR for ED was 2.7 (95% CI=1.8–3.9) for those with severe depressive symptoms, and 1.9 (95% CI=1.3–2.7) for current/former smokers with low depressive symptoms.

8 This article underlines the interplay of clinical and psychological factors for determining the risk of ED in type 2 diabetes, and can help to identify patients in whom much greater attention is needed to detect erectile problems.

Berardis Gd, Pellegrini F, Franciosi M et al (2003) Identifying patients with type 2 diabetes with a higher likelihood of erectile dysfunction: the role of the interaction between clinical and psychological factors. *Journal of Urology* **169**: 1422–8

JOURNAL OF UROLOGY



Successful ED treatment improves quality of life

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓

- 1 ED has a broad, negative impact on health-related quality of life.
- 2 This study assessed the effect of therapy for ED on 1-year, health-related, quality-of-life outcomes using a validated instrument that is disease-specific.
- 3 Using an observational ED registry, clinical, sociodemographic and health-related, quality-of-life information was collected at baseline, and 3, 6 and 12 months later. Only men who were undergoing ED treatment were included in this analysis.

4 Of the 89 patients in the study, 40 (45%) responded to therapy by International Index of Erectile Function criteria (responders). Responders and non-responders had comparable baseline disease severity and health-related quality of life.

5 At 1 year, responders reported significantly better health-related quality of life and greater improvement from baseline in sexual experience than non-responders (mean change -1.64 vs 3.19) and emotional life (mean -3.01 vs 1.75) domains of the Psychological Impact of Erectile Dysfunction scales ($P < 0.01$). This 4.5–5-point difference in mean change score was considered moderately clinically significant.

6 Men who respond to ED treatment report significantly better health-related quality of life 1 year after initial presentation for ED than non-responders.

7 This finding underlines the importance in diagnosing and treating ED, as successful therapy improves health-related quality of life in affected men.

Latini DM, Penson DF, Lubeck DP et al (2003) Longitudinal differences in disease-specific quality of life in men with erectile dysfunction: results from the exploratory comprehensive evaluation of erectile dysfunction study. *Journal of Urology* **169**: 1437–42

UROLOGIC CLINICS OF NORTH AMERICA



Urologists are at the frontline in treating diabetic complications

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓✓✓

- 1 This article reviews the complications of diabetes in urology (i.e. diabetic cystopathy and ED), and discusses future treatment strategies for these complications.
- 2 Diabetic cystopathy is characterised by impaired sensation of bladder fullness, increased bladder capacity, reduced bladder contractility and increased residual urine.
- 3 Diabetic cystopathy is recognised as a frequent complication of diabetes, although it often develops insidiously, and symptoms do not appear until the disease is in an advanced stage.

4 The treatment for diabetic cystopathy is to avoid or eliminate residual urine. In the future, neurotrophic factors or other growth factors combined with targeted gene therapy techniques may be beneficial for the therapy of patients with diabetic cystopathy.

5 Most urologists are aware that ED is a frequent complication of diabetes and is usually of organic origin.

6 ED induced by diabetes is often composed of endocrinologic, neurogenic and vasculogenic components. Hence, evaluations for each component are needed.

7 Treatments include vacuum erection devices, oral drugs, such as sildenafil, and intracavernous injection of vasoactive agents.

8 The tremendous success of sildenafil has encouraged the development of other drugs to treat ED. Additionally, treating diabetic ED with neurotrophic factors may be a logical future strategy.

9 Urologists are at the frontline in the diagnosis and treatment of the complications of diabetes. More awareness is needed to improve our understanding of diabetic complications in urology.

Sasaki K, Yoshimura N, Chancellor MB (2003) Implications of diabetes mellitus in urology. *Urologic Clinics of North America* **30**: 1–12