International Journal of Impotence Research (2008) 20, 501–506

0955-9930/08 $30.00
www.nature.com/ijir

ORIGINAL ARTICLE

Does cardiovascular risk reduction alleviate erectile dysfunction in men with type II diabetes mellitus?

SAM Khatana[1], TH Taveira[1,2], MM Miner[3], CB Eaton[4] and W-C Wu[1,5]

[1]*Target Research Enhancement Program, Providence Veterans Affairs Medical Center, Providence, RI, USA;* [2]*College of Pharmacy, University of Rhode Island, Kingston, RI, USA;* [3]*Department of Family Medicine, Men's Health Center, Miriam Hospital, Warren Alpert Medical School of Brown University, Providence, RI, USA;* [4]*Department of Family Medicine, Memorial Hospital of Rhode Island, Warren Alpert Medical School of Brown University, Providence, RI, USA and* [5]*Department of Medicine, Providence Veterans Affairs Medical Center, Warren Alpert Medical School of Brown University, Providence, RI, USA*

Veterans ($N=41$) with type II diabetes were enrolled in a behavioral and pharmacologic intervention for cardiac risk reduction for 4 weeks at the Providence Veterans Affairs Medical Center during 2004–2007 and were followed up 3 months post intervention. Erectile dysfunction (ED) was assessed using the 5-item version of the International Index of Erectile Function (IIEF-5). Participants experienced significant improvements in hemoglobin A1c (HbA1c), diastolic blood pressure and total cholesterol levels over the course of the intervention. Change in systolic and diastolic blood pressure and reduction in or maintenance of HbA1c below 7.0% were significantly associated with change in IIEF-5 ($P=0.01$, $P=0.01$, $P=0.04$, respectively). These results suggest that improved blood pressure and glycemic control in men with diabetes may lead to an improvement in ED.
International Journal of Impotence Research (2008) **20,** 501–506; doi:10.1038/ijir.2008.36; published online 31 July 2008

Keywords: erectile dysfunction; diabetes mellitus; type II; hemoglobin A1c

Introduction

Erectile dysfunction (ED) and cardiovascular disease are highly prevalent among men with diabetes. An estimated 20–85% of diabetic men have some form of ED[1] and are three times more likely to suffer from ED than nondiabetic men.[2] In addition to sharing many of the same risk factors, ED is also considered a marker for cardiovascular disease.[3] Risk factors such as elevated hemoglobin A1c (HbA1c), blood pressure (BP) and hyperlipidemia/dyslipidemia have been associated with both cardiovascular disease[4,5] and ED in patients with diabetes.[1,6–9]

Previous studies have shown a beneficial effect on ED of reduction in certain cardiovascular risk factors such as body mass index (BMI), cholesterol, increased physical activity, reduced BMI and smoking cessation in nondiabetic men.[10–13] However, data are lacking on the effect of changing multiple cardiovascular risk factors on ED among men with diabetes. This is one of the first studies to assess the impact of multifactorial cardiovascular risk reduction on ED in men with diabetes. Thus, we studied the effects of an intensive behavioral and pharmacological intervention targeting hyperglycemia, hypertension and hyperlipidemia on ED in a cohort of diabetic men.

Methods

Design

This is a retrospective analysis of the study 'Combined Behavioral and Pharmacological Intervention for Cardiovascular Risk Reduction in Diabetic Patients (ClinicalTrials.gov Identifier: NCT00357955)', where 109 participants were randomly assigned to receive an intensive behavioral and pharmacological group intervention, 'Multidisciplinary Education in Diabetes and Intervention for Cardiac risk reduction (MEDIC)' program ($n=58$), or continue their usual care ($n=51$) at the Providence Veterans Affairs Medical Center during

Correspondence: Dr W-C Wu, Providence Veterans Affairs Medical Center, 830 Chalkstone Ave., Providence, RI 02908, USA.
E-mail: Wen-Chih.Wu@va.gov
Received 16 May 2008; revised 24 June 2008; accepted 28 June 2008; published online 31 July 2008

2004–2007. The protocol received approval from the Institutional Review Board at the Providence Veterans Affairs Medical Center.

Intervention
Participants in the treatment arm attended weekly group sessions of MEDIC for 1 month, where clinical pharmacists provided education and behavioral modification to encourage diet, exercise and disease self-management, tobacco cessation and other co-morbid risk reduction. Medication titration followed an algorithm to achieve tobacco cessation, glycemic, BP and lipid control. All participants returned for follow-up 3 months post intervention (4-month follow-up).

Data collection
Erectile dysfunction was assessed using the self-reported 5-item version of the International Index of Erectile Function (IIEF-5)[14] at the beginning of the study and at the 4-month follow-up. We collected demographic factors, medical history and medication usage. All participants were assessed for weight, BP, HbA1C and lipids levels at the baseline of the study and again at the 4-month follow-up.

Subjects
Participants in the study were veterans, 18 years and older, with type II diabetes and an elevated HbA1c of 7–9% at least 6 months prior to the start of the study. Recruitment occurred at the Providence Veterans Affairs Medical Center from 2004–2007. The focus of the current analysis is restricted to the participants assigned to the treatment arm who completed the IIEF-5 at baseline and at the 4-month follow-up ($n = 41$).

Risk-factor goals
HbA1c, BP and total cholesterol (TC) were assigned cutoff levels based on the Framingham coronary disease prediction algorithm[4] and the American Diabetes Association standards of medical care.[15] Participants were determined to have met goals for each of the risk factors if they achieved or maintained a level below the cutoff level. Cutoff levels were determined for HbA1c, BP and TC as follows:

(a) Hemoglobin A1c: 7.0%
(b) Blood pressure: 130/80 mm Hg
(c) Total cholesterol: 160 mg per 100 ml.

Analyses
The distribution of different outcome variables was examined using the Shapiro–Wilk *W* test. If a deviation from normality was found, log transformation of the data points was performed and analyses were then performed for the variables on its original and log transformed states. If there was no difference in outcome of analysis between original and log transformed states, the original values were reported. All measured risk factors and medication use were compared between baseline and follow-up using paired Student's *t*-tests or two-tail Fisher's exact tests. First, change in IIEF-5 was modeled using univariate linear regression with change in systolic and diastolic BP, HbA1c and TC. Then change in IIEF-5 scores was compared among participants who did and did not meet each of the risk-factor goals. We compared demographics, co-morbidities and medication use among people who did and did not meet each of the goals to assess for potential confounding factors. Change in IIEF-5 was then modeled with change in risk factors and risk-factor goals after adjusting for these confounding factors. To compare the effect of meeting multiple goals vs one vs zero goals on erectile function, we used Student's *t*-test for each pair. Only goals that showed an increase in IIEF-5 score were included in the latter analysis. All statistical analyses were conducted using SAS JMP (SAS Institute Inc., Cary, NC, USA). Statistical significance was defined as $P < 0.05$. Data are presented as mean ± s.d.

Results

A total of 41 men completed the IIEF-5 at both baseline and the 4-month follow-up. Characteristics of the participants are shown in Table 1. The mean age of the participants was 62.4 ± 9.7 years and 85.4% were white. There was a high prevalence of coronary artery disease (53.7%) and one-third of the participants were active smokers. There was a significant decrease from baseline in the levels of HbA1c, TC and diastolic BP at the 4-month follow-up. However, there was no change in the

Table 1 Demographic and clinical characteristics of participants ($n = 41$)

Age	62.4 ± 9.7 years
Race	
White	85.4%
Black or African American	9.7%
Unknown	4.9%
Clinical variables	
Active smokers	36.6%
History of coronary artery disease	53.7%
Homocysteine	11.8 ± 3.7 $\mu mol\, l^{-1}$
C-reactive protein	5.9 ± 4.8 $mg\, l^{-1}$
Testosterone	3.1 ± 1.5 $ng\, ml^{-1}$

mean IIEF-5 score over that period (Table 2). There was no significant change in the categories of medication use before and after the intervention (Table 3).

In univariate linear regression, there was a significant association between change in systolic and diastolic BP and change in IIEF-5 ($r = 0.4$, $P = 0.01$; $r = 0.4$, $P = 0.01$, respectively) whereas change in HbA1c and TC did not have any significant association ($r = 0.02$, $P = 0.9$; $r = 0.2$, $P = 0.6$, respectively). The number of people who met assigned goals in HbA1c, BP and TC were 16, 22 and 28, respectively (39.0, 53.7, 68.3%, respectively; Table 4). Participants who met HbA1c goals experienced a statistically significant improvement in IIEF-5 compared to participants not meeting the goal (1.6 ± 3.7 vs −1.0 ± 4.0, $P = 0.04$) over the 4-month period. Participants meeting the BP goal also experienced a small improvement in IIEF-5 compared to participants not meeting the goal, who experienced a decline (0.6 ± 4.4 vs −0.6 ± 3.5, $P = 0.3$). Participants meeting the TC goal experienced no change in their mean IIEF-5 score whereas there was a slight increase seen among patients not meeting the goal (0.0 ± 4.7 vs 0.1 ± 2.3, $P = 1.0$; Figure 1).

There was no significant difference in race, age, smoking status or testosterone levels between participants who did and did not meet goals for HbA1c, BP and TC. The only significant difference in medication usage between participants who did and did not meet each of the three goals was in sulfonylurea and insulin use for the BP goal ($P = 0.004$, $P = 0.01$, respectively; Table 4). However, there was an increasing trend in PDE5 inhibitor use for participants who met HbA1c and BP goals (12.5–25.0%, $P = 0.7$ and 4.6–13.6%, $P = 0.6$, respectively) and for participants who failed to meet the TC goal (15.4–30.8% $P = 0.6$) from baseline to the 4-month follow-up. The average change in IIEF-5 among people who started using a PDE5 inhibitor over the course of the intervention was −0.3 ± 1.2, $P = 0.9$. Change in IIEF-5 was modeled using multiple linear regression adjusted first for age and then for PDE5 inhibitor use. Changes in systolic and diastolic BP were still significant predictors of change in IIEF-5 after adjusting for age ($P = 0.01$ and $P = 0.01$, respectively) and change in PDE5 inhibitor use ($P = 0.01$ and $P = 0.01$, respectively; Table 5). HbA1c goal also remained a significant predictor of change in IIEF-5 after adjusting for age ($P = 0.05$) and change in PDE5 inhibitor use ($P = 0.05$).

Participants who had met goals for both BP and HbA1c experienced the greatest improvement in IIEF-5 (2.2 ± 1.6) followed by participants who met only one of the goals (BP or HbA1c) (−0.05 ± 0.8), and then by those meeting none of the goals (−1.5 ± 1.2). There was a significant difference between participants who had met two and zero goals ($P = 0.04$), but no difference between participants meeting two and one goals ($P = 0.2$) or between one and zero goals ($P = 0.3$). There was a nonsignificant moderate correlation between change in IIEF-5 and the number of goals met ($r = 0.3$, $P = 0.1$; Figure 2).

Table 3 Medication use

Medication (n = 41)	*Baseline (%)*	*After 4 months (%)*
Metformin	56.1	56.1
Sulfonylureas	68.3	65.9
Thiazolidinediones	41.5	58.5
Insulin	48.8	58.5
β-Blockers	65.9	68.3
ACE inhibitors	58.5	68.3
Angiotensin receptor blockers	24.4	29.3
Diuretics	56.1	56.1
Nitrates	12.2	17.1
Statins	95.1	92.7
Antidepressants	34.2	36.6
PDE5 inhibitor	9.8	14.6

No statistically significant difference between baseline and 4-month follow-up.

Table 2 Change in measured factors over 4 months

(n = 41)	*Baseline*	*Final*	*Difference*
IIEF-5	12.2 ± 6.5	12.2 ± 6.4	0.02 ± 4.0
BMI	34.1 ± 6.3	34.0 ± 6.3	−0.1 ± 1.3
Systolic BP	133.6 ± 19.6 mm Hg	126.2 ± 15.0 mm Hg	−7.3 ± 22.6 mm Hg
Diastolic BP	75.0 ± 11.2 mm Hg	69.8 ± 10.9 mm Hg	−5.1 ± 10.6 mm Hg*
Hemoglobin A1c	8.1 ± 1.6%	7.3 ± 0.9%	−0.8 ± 1.0%*
Total cholesterol	173.2 ± 45.8 mg per 100 ml	152.8 ± 29.5 mg per 100 ml	−20.4 ± 39.7 mg per 100 ml*
HDL	38.9 ± 10.3 mg per 100 ml	39.7 ± 13.2 mg per 100 ml	0.8 ± 11.9 mg per 100 ml
LDL	94.4 ± 34.6 mg per 100 ml	83.0 ± 23.6 mg per 100 ml	−11.3 ± 33.2 mg per 100 ml
Triglycerides	191.6 ± 114.5 mg per 100 ml	163.3 ± 81.7 mg per 100 ml	−28.4 ± 79.6 mg per 100 ml

Abbreviations: BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; IIEF-5, 5-Item version of the International Index of Erectile Function; LDL, low-density lipoprotein.
*$P < 0.05$ from baseline.

Table 4 Medication use at 4-month follow-up

	Blood pressure goal		*Hemoglobin A1c goal*		*Total cholesterol goal*	
	Goal met (%) (n = 22)	*Goal not met (%) (n = 19)*	*Goal met (%) (n = 16)*	*Goal not met (%) (n = 25)*	*Goal met (%) (n = 28)*	*Goal not met (%) (n = 13)*
Metformin	45.5	68.4	43.8	64.0	60.7	46.2
Sulfonylureas	45.5*	89.5*	56.3	72.0	67.9	61.5
Thiazolidinediones	63.6	52.6	56.3	60.0	57.1	61.5
Insulin	77.3*	36.8*	50.0	64.0	57.1	61.5
β-Blockers	77.3	57.9	75.0	64.0	75.0	53.9
ACE inhibitors	59.1	79.0	75.0	64.0	64.3	76.9
Angiotensin receptor blockers	31.8	26.3	25.0	32.0	32.1	23.1
Diuretics	59.1	52.6	56.3	56.0	53.6	61.5
Nitrates	18.2	15.8	31.3	8.0	21.4	7.7
Statins	95.5	89.5	93.8	92.0	92.9	92.3
Antidepressants	40.9	31.6	37.5	36.0	28.6	53.9
PDE5 inhibitor	13.6	15.8	25.0	8.0	7.1	30.8

*$P < 0.05$ between goal met and not met groups.

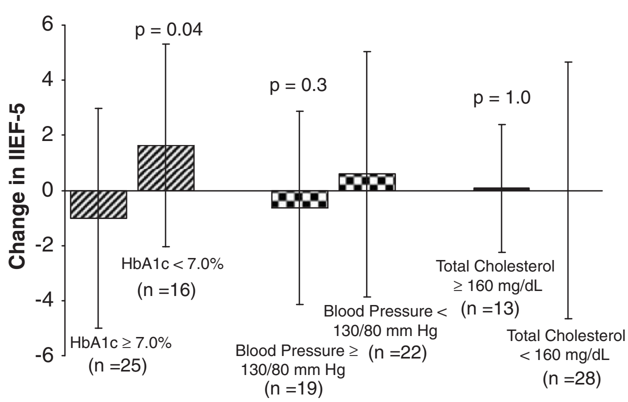

Figure 1 Change in IIEF-5 at 4-month follow-up for meeting risk-factor goals. ▨ Hemoglobin A1c, ▣ Blood pressure, ■ Total cholesterol. Error Bars represent s.d.

Discussion

This is one of the first studies relating the isolated and combined effects of reduction in BP, HbA1c and TC levels to ED. Change in systolic and diastolic BP and a reduction in or maintenance of HbA1c below 7.0% were significantly associated with change in IIEF-5 score from baseline to the 4-month follow-up. Additionally there also appeared to be an additive effect as participants who met both HbA1c and BP goals improved to a greater degree than those meeting either only one of the goals or none of the goals.

Elevated HbA1c levels have been shown to be associated with ED.[1] In animal models, hyperglycemia leads to decreased Nitrous oxide (NO) production.[16] Thus, a decrease in glycemia may allow for increased NO production leading to improved vasodilatation and erectile function. Hypertension is also highly prevalent among diabetic men with ED.[17] Hypertension is most likely related to ED being a primary vascular risk factor and the resulting long-term vascular damage.[18] Although treatment of hypertension with common antihypertensive medications has been associated with ED,[19,20] another study also showed recovery of erectile function after brief aggressive antihypertensive therapy.[21] Moreover, antihypertensives at levels currently used in clinical settings are not likely to negatively influence ED significantly.[22] Our results suggest that although it may be important to lower HbA1c levels below a clinically important threshold to experience improvement in ED, any reduction in BP may also provide beneficial effects. Additionally, as hyperglycemia and hypertension may affect ED through different mechanisms, improvement in both appears to lead to the greatest improvement in ED.

The role of lipid lowering and the use of statins in ED is controversial. Although one previous study has shown a decrease in TC accompanied with an improvement in ED following statin therapy,[11] another study showed a reduction in IIEF-5 scores following statin therapy.[23] It is possible that the reduction in TC in our study may have been through a manner which does not affect diabetic ED. Our intervention did not result in a significant change in high-density lipoprotein (HDL) or triglyceride levels, both of which have been associated with poor sexual function.[6,24,25] Our finding of lowering of TC without significant changes in HDL and triglycerides is typical of statins and especially of simvastatin, which was the preferred statin used at the study institution.[26] The short time frame of our intervention makes it likely that the gains in risk-factor control were largely reflective of the weekly medication up titrations, and less from the behavioral modifications which often take longer time for their effects to be observed.[10] Lastly, it may also be possible that in men with diabetes, the effect of TC on ED is minimal compared to that exerted

Table 5 Age- and PDE5 inhibitor use-adjusted linear regression

(n = 41)	Age adjusted		PDE5 inhibitor use (4-month follow-up) adjusted	
	Estimate	P	Estimate	P
Change in systolic blood pressure	−0.1	0.01*	−0.1	0.01*
Change in diastolic blood pressure	−0.1	0.01*	−0.2	0.01*
Change in HbA1c	0.1	0.9	0.1	0.9
Change in total cholesterol	0.02	0.3	0.02	0.3
Blood pressure goal	0.7	0.3	0.6	0.3
HbA1c goal	1.3	0.05*	1.3	0.05*
Total cholesterol goal	−0.1	0.9	−0.1	0.9

Abbreviation: HbA1c, hemoglobin A1c.
*$P<0.05$.

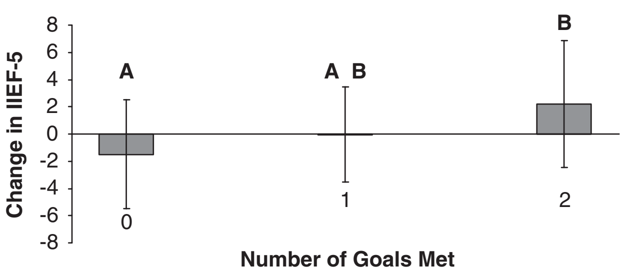

Figure 2 Change in IIEF-5 at 4-month follow-up for meeting multiple risk-factor goals. Error Bars represent s.d. Levels not connected by the same letter are significantly different.

by other factors such as hyperglycemia and hypertension.

Our study was limited by the small sample size resulting in reduced statistical power. Despite this shortcoming, we were able to see a statistically significant association between change in IIEF-5 and meeting the HbA1c goal and change in systolic and diastolic BP. A greater number of participants may allow us to stratify our goals to determine the effects of meeting multiple ED comorbidity goals and at different levels rather than at a singular cutoff point. We were also limited by the nonexperimental design, which may result in selection bias. However, to date very few studies have addressed the role of multifactorial cardiac risk reduction in improving the ED of diabetic men, and our data may provide the much-needed pilot data for the design of larger randomized controlled studies. The changes seen in IIEF-5 were relatively small, and may not be biologically meaningful. Given the short duration of our study, we believe that any change observed is important as it may suggest that more intensive and longer lasting interventions may result in greater changes in IIEF-5. In addition, the magnitude of the IIEF-5 changes were additive. A longer follow-up may also help to determine the longevity of the improvements in both the cardiovascular risk factors and the change in ED. Lastly, as the study employed the IIEF-5 questionnaire, the limitations inherent in the IIEF-5, such as focus on heterosexual sex, lack of inquiry regarding desire and lack of information on the etiology of the disorder[27] were a part of this study.

Although studies have been done on the prevalence of ED risk factors among men with diabetes,[18,28] there have been no previous studies examining the impact of reducing multiple cardiovascular risk on ED among diabetic men. Our study provides the first evidence of the beneficial effect of BP control and reduction and maintenance of a low HbA1c on ED in men with diabetes.

Financial disclosure

The authors state no conflict of interest.

References

1 Romeo JH, Seftel AD, Madhun ZT, Aron DC. Sexual function in men with diabetes type 2: association with glycemic control. *J Urol* 2000; **163**: 788–791.
2 Feldman HA, Goldstein I, Gatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts male aging study. *J Urol* 1994; **151**: 54–61.
3 Ponholzer A, Temml C, Obermayr R, Wehrberger C, Madersbacher S. Is erectile dysfunction an indicator for increased risk of coronary heart disease and stroke? *Eur Urol* 2005; **48**: 512–518.
4 Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998; **97**: 1837–1847.
5 Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR *et al.* Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med* 2004; **141**: 421–431.
6 Wei M, Macera CA, Davis DR, Hornung CA, Nankin HR, Blair SN. Total cholesterol and high density lipoprotein cholesterol as important predictors of erectile dysfunction. *Am J Epidemiol* 1994; **140**: 930–937.
7 Burchardt M, Burchardt T, Baer L, Kiss AJ, Pawar RV, Shabsigh A *et al.* Hypertension is associated with severe erectile dysfunction. *J Urol* 2000; **164**: 1188–1191.
8 Miyata Y, Shindo K, Matsuya F, Noguchi M, Nishikido M, Koga S *et al.* Erectile dysfunction in hemodialysis patients

with diabetes mellitus: association with age and hemoglobin A1c levels. *Int J Urol* 2004; **11**: 530–534.
9 Ahn TY, Park JK, Lee SW, Hong JH, Park NC, Kim JJ *et al.* Prevalence and risk factors for erectile dysfunction in Korean men: results of an epidemiological study. *J Sex Med* 2007; **4**: 1269–1276.
10 Esposito K, Giugliano F, Di Palo C, Giugliano G, Marfella R, D'Andrea F *et al.* Effect of lifestyle changes on erectile dysfunction in obese men: a randomized controlled trial. *JAMA* 2004; **291**: 2978–2984.
11 Saltzman EA, Guay AT, Jacobson J. Improvement in erectile function in men with organic erectile dysfunction by correction of elevated cholesterol levels: a clinical observation. *J Urol* 2004; **172**: 255–258.
12 Guay AT, Perez JB, Heatley GJ. Cessation of smoking rapidly decreases erectile dysfunction. *Endocr Pract* 1998; **4**: 23–26.
13 Derby CA, Mohr BA, Goldstein I, Feldman HA, Johannes CB, McKinlay JB. Modifiable risk factors and erectile dysfunction: can lifestyle changes modify risk? *Urology* 2000; **56**: 302–306.
14 Rosen RC, Cappelleri JC, Smith MD, Lipsky J, Peña BM. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. *Int J Impot Res* 1999; **11**: 319–326.
15 American Diabetes Association. Standards of medical care in diabetes—2008. *Diabetes Care* 2008; **31**: S12–S54.
16 Du XL, Edelstein D, Dimmeler S, Ju Q, Sui C, Brownlee M. Hyperglycemia inhibits endothelial nitric oxide synthase activity by posttranslational modification at the Akt site. *J Clin Invest* 2001; **108**: 1341–1348.
17 Siu SC, Lo SK, Wong KW, Ip KM, Wong YS. Prevalence of and risk factors for erectile dysfunction in Hong Kong diabetic patients. *Diabet Med* 2001; **18**: 732–738.
18 Burchardt M, Burchardt T, Baer L, Kiss AJ, Pawar RV, Shabsigh A *et al.* Hypertension is associated with severe erectile dysfunction. *J Urol* 2000; **164**: 1188–1191.
19 Wein AJ, Van Arsdalen K. Drug induced male sexual dysfunction. *Urol Clin North Am* 1988; **15**: 23.
20 Francis ME, Kusek JW, Nyberg LM, Eggers PW. The contribution of common medical conditions and drug exposures to erectile dysfunction in adult males. *J Urol* 2007; **178**: 591–596.
21 Hale TM, Okabe H, Bushfield TL, Heaton JP, Adams MA. Recovery of erectile function after brief aggressive antihypertensive therapy. *J Urol* 2002; **168**: 348–354.
22 Thomas DR. Medications and sexual function. *Clin Geriatr Med* 2003; **19**: 553–562.
23 Solomon H, Samarasinghe YP, Feher MD, Man J, Rivas-Toro H, Lumb PJ *et al.* Erectile dysfunction and statin treatment in high cardiovascular risk patients. *Int J Clin Pract* 2006; **60**: 141–145.
24 Pinnock CB, Stapleton AM, Marshall VR. Erectile dysfunction in the community: a prevalence study. *Med J Aust* 1999; **171**: 353–357.
25 Roumeguère T, Wespes E, Carpentier Y, Hoffmann P, Schulman CC. Erectile dysfunction is associated with a high prevalence of hyperlipidemia and coronary heart disease risk. *Eur Urol* 2003; **44**: 355–359.
26 Pedersen TR, Olsson AG, Faergeman O, Kjekshus J, Wedel H, Berg K *et al.* Lipoprotein changes and reduction in the incidence of major coronary heart disease events in the Scandinavian Simvastatin Survival Study (4S). *Circulation* 1998; **97**: 1453–1460.
27 Rosen RC, Cappelleri JC, Gendrano III N. The International Index of Erectile Function (IIEF): a state-of-the-science review. *Int J Impot Res* 2002; **14**: 226–244.
28 Fedele D, Coscelli C, Cucinotta D, Forti G, Santeusanio F, Viaggi S *et al.* Incidence of erectile dysfunction in Italian men with diabetes. *J Urol* 2001; **166**: 1368–1371.