Can simvastatin improve erectile function and health-related quality of life in men aged ≥40 years with erectile dysfunction? Results of the Erectile Dysfunction and Statins Trial [ISRCTN667729971]

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What's known on the subject? and What does the study add?

- Erectile dysfunction (ED) is often associated with endothelial dysfunction. It is also recognized as a marker for underlying vascular disease. There are missed opportunities to address cardiovascular risk factors in these men.
- Simvastatin administered for 6 months improves sexual health-related quality of life in men aged ≥40 years with untreated ED. It reduces the risk of future cardiovascular events via a reduction in serum cholesterol in men with ED. A non-significant trend towards improving erectile function suggests longer trials with a more potent statin may be required. There is high probability (>80%) of simvastatin being cost-effective in men with ED. Enquiry about erectile function provides the opportunity to address cardiovascular risk factors.

Objective

- To evaluate the effectiveness and cost-effectiveness of simvastatin on erectile function and health-related quality of life in men aged ≥40 years with erectile dysfunction (ED).

Patients and Methods

- ED is common in men aged ≥40 years and impacts upon their overall health-related quality of life and that of their partners.
- Men aged ≥40 years who were not receiving lipid lowering or anti-hypertensive medication and not at high cardiovascular risk were recruited from 10 general practices in the East of England.
- In total, 173 eligible men with untreated ED were randomized to double-blind treatment with 40 mg of simvastatin or placebo once daily for 6 months. Data were collected at three points over 30 weeks.
- The main outcome was erectile function (International Index of Erectile Function-5 score). Secondary outcomes included male ED-specific quality of life (MED-QoL), quality-adjusted life years (QALYs) using the generic Euroqol measure (EQ-5D), endothelial function, cardiovascular risk, cholesterol and health service costs.

Results

- There was no significant difference in erectile function between the simvastatin and placebo groups (mean change, 1.28 vs 0.07, $z = 1.1$, $p = 0.27$), although a significant improvement in MED-QoL was observed (5% vs 2%, $z = 2.09$, $p = 0.04$).
- Both 10-year cardiovascular risk and low-density lipoprotein were reduced (cardiovascular risk, $z = -3.67$, $p < 0.001$; low-density lipoprotein, $z = -5.46$, $p < 0.001$), with no consistent change in endothelial function.
- The frequency of sexual encounters is correlated with improved erectile function.
- The joint distribution of costs and QALY benefits indicates that the probability of simvastatin being cost-effective for willingness-to-pay thresholds of £20 000 and £30 000 is 86% and 83%, respectively.

Conclusions

- Identifying men with ED provides an opportunity to modify future cardiovascular risk and to improve MED-QoL by treating them with 40 mg of simvastatin.
- The joint analysis of costs and QALY benefits suggests that there is high probability that simvastatin is a cost-effective strategy in men with ED.

- The findings could influence urological and primary care practice by including questions on ED during routine consultations and relevant clinical protocols. This provides an opportunity to impart lifestyle advice.

Keywords

erectile dysfunction, randomized controlled trial, statins

Introduction

Erectile dysfunction (ED) is the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual intercourse. Estimates of prevalence vary [1–5], ranging from 52% in men aged 40–70 years to 10% in men aged 18–59 years in the USA [1,3]. In the UK, 26% of men aged 18–75 years had current ED, with 39% reporting they had ED at some time [4]. A conservative estimate of prevalence in the 15.5 million men aged ≥40 years in the UK is 20% (i.e. 3.1 million cases). The US Prostate Cancer Prevention Trial reported ED in 47% of men aged ≥55 years who had no cardiovascular disease (CVD) [5]. A reasonable estimate is that one-third of men will experience ED at some time.

ED has a major impact on sexual and mental health [3,6] but the consultation rates for ED are low [4,7]. Although the availability of sildenafil and other phosphodiesterase inhibitors has increased the proportion seeking help [7], these drugs are expensive and, in the UK NHS, their use is limited to conditions such as diabetes, prostate cancer surgery or Parkinson's disease [8,9]. Sildenafil will lose its exclusivity in 2013.

ED shares risk factors with CVD [10–14] and is linked to high total and low-density lipoprotein (LDL) cholesterol [15–17], as well as endothelial dysfunction. It is suggested that ED related to reduced blood flow in the small penile arteries may be a predictor of later vascular disease occurring in larger arteries such as the coronary vasculature [12,13,15,18]. Recent consensus meetings concur that ED is either a predictor of future CVD or an early marker of silent atherosclerotic CVD [12,13].

Sildenafil is effective, although not all patients respond [19]. Statins can improve endothelial function rapidly before affecting the lipid profile [15,16,20].

However large-scale lipid studies have not assessed whether effective lipid lowering affects ED. A small observational study in nine men reported a significant reduction in ED after 3 months of atorvastatin [15]. A placebo-controlled randomized trial in 12 men who were non-responders to sildenafil suggested that atorvastatin improved sexual function and the response to sildenafil [21]. By contrast, another small study reported increased ED after 6 months of statin treatment, although the population comprised men at high risk of CVD receiving other medication, which could itself increase ED [22]. Erectile function can be improved by correcting serum cholesterol concentrations with atorvastatin, although only in patients who have hypercholesterolaemia as a risk factor for erectile dysfunction [23]. Patients with a significantly high ratio total/high-density lipoprotein cholesterol (>7.5) were excluded from the Erectile Dysfunction and Statins Trial.

It is not known whether the action of statins to improve endothelial function and blood flow may, as a consequence, improve ED. If simvastatin were effective and, over the long term, prevented CVD, there would be major health benefits for the patient, as well as potential savings for the health economy.

The present study reports the results of a randomized controlled trial evaluating the effectiveness and cost-effectiveness of simvastatin therapy in men with ED. The primary aim was to establish whether, in men with untreated ED but no other significant cardiovascular risk factors, lowering LDL cholesterol with simvastatin improves erectile function as measured by the five-item version of the International Index of Erectile Function (IIEF-5). The secondary aims were to evaluate its effects on sexual health-related quality of life (HRQL), long-term risk of CVD, lipid profile, endothelial function and health service costs.

The rationale, design and detailed methodology of the present study have been reported previously in the trial protocol [24].

Patients and Methods

A double-blind randomized controlled trial comparing treatment with simvastatin or placebo on ED was conducted in 10 general practices in the East of England [24]. The study protocol was approved by the Essex 1 Research Ethics Committee and clinical trial authorization was obtained from the UK Medicines and Healthcare Products Regulatory Agency.

In total, 173 eligible men aged ≥40 years with untreated ED (score < 22 on the IIEF), and no other cardiovascular risk factors were randomized to receive 40 mg of simvastatin or placebo once daily for 6 months. Exclusions were based on participants' medical and drug history and those considered by the GP to be unsuitable, such as those at significant CVD risk requiring statin treatment.

Randomization to active simvastatin or placebo was on a 1:1 basis and was computer-generated at the Clinical Trials Co-ordinating Centre. A study nurse from the participating site contacted the centre giving the participant study number, which contained the practice identifier, date of birth as a check and IIEF-5 score from the baseline visit. The IIEF-5 score, categorized as severe (score from 5 to 11) and mild/moderate (score from 12 to 21) and the general practice were used as minimization criteria in the randomization. Packages of medication (seven bottles of 28 tablets per bottle per package), prelabelled so that placebo and active looked identical, were stored in a locked cabinet in the general practice. The nurse was informed about which numbered medication to allocate and inserted the participant study number, date and name of the general practice to the labels on each bottle and the outer packaging. After randomization, participants either collected or received a package in the post containing 24 weeks of medication.

Data were collected at baseline, and at 3 and 6 months. Participants completed the IIEF-5 questionnaire, the male ED-specific quality of life (MED-QoL) questionnaire and the generic Euroqol EQ-5D questionnaire (baseline and 6 months) [25–27]. Sexual encounter profile (SEP) diaries were completed at three time points. Data on NHS use over the previous 3 months were collected for economic analysis.

Fasting blood samples were taken for total, LDL, high-density lipoprotein cholesterol, glucose, liver function tests, renal function and testosterone. Endothelial function was assessed in a subsample of 12 participants at baseline and at the end of the trial by the ratio of the augmentation index when patients were treated with salbutamol relative to glyceryltrinitrate. A larger percentage fall from baseline to the close of trial would indicate improved endothelial function [28]. Safety was assessed by recording adverse events and carrying out a regular review during trial visits.

Outcomes and Methods of Analysis

Sample size estimations were based on the ability to detect a clinically relevant improvement of three points on the IIEF-5 (an improvement in score of one point in three of the five questions) [24]. Assuming $\alpha = 0.05$, $N = 173$ provided 90% power and $N = 126$ provided 80% power. The primary outcome was the change in erectile function, using an intention-to-treat analysis. Secondary outcomes included CVD risk, LDL cholesterol, testosterone, MED-QoL, and sexual encounter success and satisfaction (SEP diaries). These outcomes were evaluated using a general linear model (with visit clustered within patients, and including treatment arm and severity of ED, interaction terms for treatment arm and visit, and treatment arm and ED severity). Baseline adjustment was included for CVD risk, testosterone and time-on-treatment. For the SEP diaries, the quality of erection and encounter satisfaction domains were evaluated using the proportion of 'yes' responses reported for each encounter. The frequency of reported attempts was estimated as the number of reported attempts divided by the number of weeks of observation. As a result of the small sample size included in the endothelial function sub-study, comparison was restricted to the use of the 95% CI and *t*-tests.

Economic evaluation was conducted as within-trial cost-utility analysis for treatment with simvastatin compared to placebo in individuals with ED over 24-week period. Health services resource use was evaluated from the NHS perspective based on GP visits, nurse visits, outpatient attendance and inpatient days. The cost of simvastatin tablets was included in the calculation. Patient-level utility was estimated using the Euroqol EQ-5D questionnaire at the start and end of the study. Quality-adjusted life years (QALYs) were calculated using the UK population tariff. To account for the correlation between costs and QALYs, a seemingly-unrelated regression model was employed. The analysis included the baseline covariates: baseline utility and cost, baseline cardiovascular risk and ED risk. Decision uncertainty was evaluated using cost-effectiveness acceptability curve (CEAC) to present the probability that simvastatin is cost-effective at different willingness-to-pay (WTP) thresholds.

Results

A total of 361 patients were invited to be screened and 173 patients were randomized (Fig. 1). There were 131 patients who completed some and 113 who completed all of the study outcome measures. Of these patients, 60 (34%) withdrew from randomized treatment, although 18 of these patients continued to complete the QoL measures. The proportion withdrawing did not depend on study arm ($\chi^2 = 0.5$, d.f. = 1, $P > 0.05$). Patients completing the study tended to be slightly older (by 3.1 years) and have higher CVD risk (by 3.2%) than patients withdrawing from randomized treatment, although they did not differ in any other way on the main baseline measures. There were minimal differences between the randomized groups. CVD risk and age were highly correlated (0.94, $p < 0.001$).

In total, 126 adverse events were reported: 19 during run in and 107 during randomized treatment. Of these, five were rated as serious but not related to the study medication. No deaths were recorded.

Table 1 shows the baseline characteristics of the randomized patients. The mean age of the patients was 56.1 years, body mass index was 27.7 kg/m^2, testosterone concentration was 15.1 nmol/L and the 10-year CVD risk

Fig. 1 Erectile dysfunction and statins trial study flow chart.

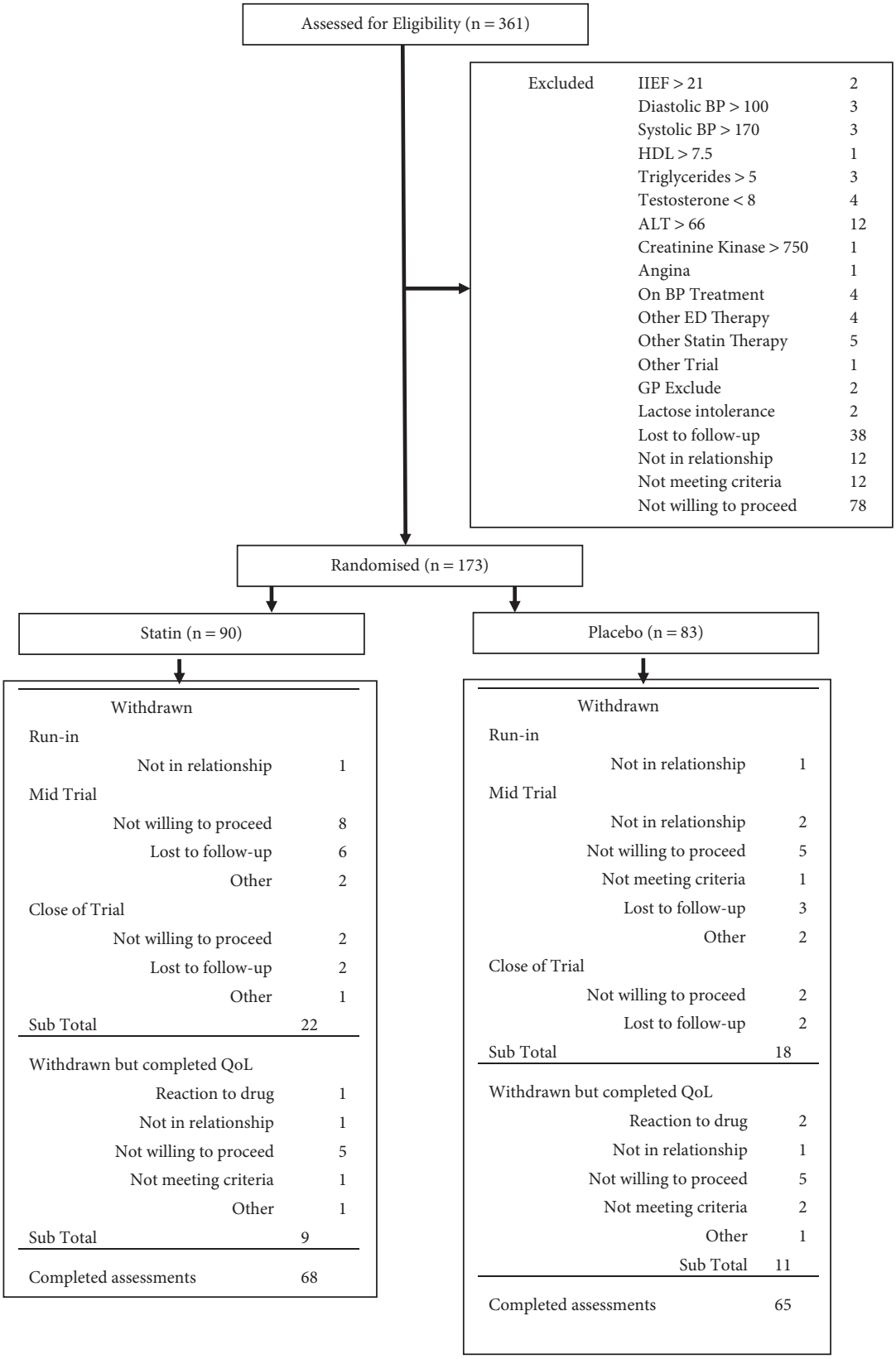


Table 1 Baseline patient characteristics and outcome measures.

Patient characteristics	Baseline								Close of trial							
	Statin				Placebo				Statin				Placebo			
	N	Mean	95% CI		N	Mean	95% CI		N	Mean	95% CI		N	Mean	95% CI	
Age (years)	90	58.0	56	60	83	54	53	56								
BMI (kg/m^2)	90	27.6	26.5	28.6	83	27.8	27	28.6								
Testosterone (nmol/L)	83	15.0	14	16	81	15.0	14	16								
Systolic BP (mmHg)	89	123.9	120.9	127.0	83	127.9	124.9	130.8								
Diastolic BP (mmHg)	89	76.7	74.9	78.5	83	80.6	78.7	82.4								
Main study outcomes																
IIEF score	90	13.0	11.7	14.2	83	14.1	13.0	15.2	64	14.02	12.3	15.8	64	14.39	12.7	16.1
Severe	34	6.59	5.4	7.8	25	8.31	6.8	9.8	25	8.32	5.7	10.9	18	10.06	6.9	13.3
Mild/moderate	56	16.82	16.0	17.7	58	16.57	15.8	17.3	39	17.67	16.2	19.1	46	16.09	14.3	17.9
MED QoL	89	0.71	0.68	0.75	79	0.71	0.68	0.74	65	0.76	0.71	0.80	64	0.73	0.69	0.78
Severe	33	0.61	0.56	0.67	22	0.61	0.56	0.66	25	0.73	0.67	0.79	18	0.67	0.59	0.74
Mild/moderate	56	0.77	0.74	0.81	57	0.75	0.71	0.78	40	0.77	0.71	0.83	46	0.76	0.70	0.81
SEP some erection	70	0.936	0.889	0.983	64	0.967	0.939	0.994	49	0.800	0.715	0.884	50	0.835	0.765	0.906
SEP satisfaction	70	0.374	0.278	0.469	64	0.372	0.277	0.468	49	0.493	0.380	0.606	50	0.441	0.327	0.555
Severe	24	0.203	0.054	0.352	17	0.215	0.057	0.373	14	0.156	0.017	0.295	13	0.410	0.147	0.673
Mild/moderate	46	0.463	0.344	0.582	47	0.429	0.314	0.545	35	0.628	0.504	0.752	37	0.452	0.320	0.583
SEP encounters (n/week)	70	0.761	0.684	0.837	64	0.820	0.697	0.944	49	0.689	0.581	0.797	50	0.613	0.520	0.705
LDL (mmol/L)	90	3.50	3.4	3.7	83	3.50	3.3	3.7	65	2.6	2.4	2.9	55	3.40	3.2	3.7
CVD risk (%)	90	9.6	5.0	15.9	81	6.3	3.9	11.8	61	10.5	6	15.4	52	7.0	3.9	12.3
Severe	34	12.3	7.4	18.5	25	7.9	4.0	11.3	24	11.8	7.6	17.5	13	9	3.9	11.3
Mild/moderate	56	8.6	4.2	14.3	56	5.5	3.75	13.3	37	10.2	4.6	13.3	39	6.2	3.9	14.2

CVD risk, mean 10-year CVD risk for a white man aged 56 years = 8.2%. For cardiovascular risk, median, 25th and 75th percentiles are reported. SEP data are reported as the proportion of 'yes' responses for first (achieved at least some erection) and fifth (satisfaction with encounter) items. The frequency of encounters is estimated as the number of reported encounters divided by the number of weeks of observation. IIEF (5–25) and MED-QoL (0–100) are scale scores. BP, blood pressure; BMI, body mass index; CVD, cardivascular disease; IIEF, International Index of Erectile Function; LDL, low-density lipoprotein; MED-QoL, male erectile dysfunction-specific quality of life; SEP, sexual encounter profile.

Table 2 Change in study outcomes from screening or baseline to close of study.

		Statin				Placebo			
		N	mean	95% CI		N	mean	95% CI	
IIEF		64	1.28	−0.03	2.59	64	0.07	−1.34	1.48
	Severe	25	1.88	−0.52	4.28	18	1.79	−0.65	4.23
	Mild/Moderate	39	0.90	−0.68	2.48	46	−0.61	−2.34	1.12
CVD Risk (%)		61	−1.46	−2.06	−0.86	52	−0.12	−0.47	0.23
LDL (mmol/L)		65	−0.93	−1.16	−0.70	55	−0.08	−0.25	0.08
MED Qol		64	0.046	0.004	0.087	61	0.017	−0.015	0.049
	Severe	24	0.117	0.067	0.167	16	0.043	−0.029	0.116
	Mild/Moderate	40	0.003	−0.053	0.059	45	0.007	−0.029	0.044
SEP Erection		45	−0.098	−0.171	−0.024	45	−0.148	−.212	−0.084
SEP Satisfaction		45	0.172	0.063	0.282	45	0.100	0.008	0.191
SEP Encounters (n/week)		45	−0.072	−0.205	0.061	45	−0.172	−0.304	−0.040
Testosterone (nmol/L)		36	−0.67	−1.58	0.24	39	−0.18	−1.33	0.97

CVD risk, mean 10-year CVD risk. SEP data are reported proportion of 'yes' responses for first (achieved at least some erection) and fifth (satisfaction with encounter) items. The Frequency of encounters is estimated as the number of reported encounters divided by the number of weeks of observation. IIEF (5–25) and MED QoL (0–100) are scale scores. CVD, cardivasculor disease; IIEF, International Index of Erectile Function; LDL, low-density lipoprotein; MED-QoL, mole erectile dysfunction-specific quality of life; SEP, sexual encounter profile.

was 8.2%. The mean IIEF score was 13.5. Data on adherence to randomized treatment were available for 117 patients, of whom 16 (eight statin, eight placebo) withdrew from randomized treatment early and took between 21% (placebo) and 42% (statin) of the medication. The remaining 101 patients took more than 70% of the randomized treatment.

Outcome data are shown in Tables 1 and 2. The improvement in IIEF as a result of statin treatment was not statistically different from placebo (1.28 vs 0.07, $z = 1.1$, $p = 0.27$). All patients with severe ED at baseline showed a larger change than patients with mild/moderate ED (1.8 and 0.08, $z = 8.5$, $p < 0.001$). Increasing cardiovascular risk significantly reduced the change in IIEF ($z = -2.21$, $p = 0.03$); a 5% increase in CVD risk reduced change by 0.45 points. There was a statistically larger improvement in MED-QoL for men on statin compared to placebo (5% vs 2%, $z = 2.09$, $p = 0.04$), which was largest for men with severe ED (12% vs 5%, $z = 4.52$, $p < 0.001$). There was no drug-specific effect for SEP erections ($z = 0.64$, $p = 0.52$) or satisfaction ($z = 0.65$, $p = 0.52$). However the proportion of reported erections fell from baseline to mid-trial (95% to 76%, $z = -4.83$, $p < 0.001$) but did not change from mid- to close of trial (76% to 82%, $z = 1.18$, $p = 0.24$). There was an increase in reported satisfaction over time ($z = 2.17$, $p = 0.03$) for all participants and patients with mild/moderate ED reported greater satisfaction than those with severe ED ($z = 2.04$, $p = 0.04$). For reported frequency of encounters (encounters/week), there was no drug specific effect ($z = 1.35$, $p = 0.18$) and no difference across IIEF Severity ($z = 1.03$, $p = 0.3$). The reported frequency of encounters fell across the duration of the study ($z = -2.66$, $p = 0.008$).

There was a weak positive correlation between the IIEF score and the frequency of encounters at close of trial but not at the baseline assessment ($r = 0.25$, $p = 0.01$ and $r = 0.14$, $p = 0.11$, respectively). There is some indication that, at close of trial, those patients attempting intercourse more than once a week report higher IIEF scores.

Both 10-year CVD risk and LDL were reduced by statin treatment compared to placebo (CVD risk, $z = -3.67$, $p < 0.001$; LDL, $z = -5.46$, $p < 0.001$). Testosterone concentrations did not change ($z = -0.31$; 95% CI, −0.69 to 1.31) and baseline testosterone was not related to any of the study outcomes (ED, $z = 1.63$, $p = 0.1$).

Only 12 of 20 patients completed the baseline and close of trial assessments for endothelial function (% change in augmentation index after dosing with salbutamol), limiting the interpretation of these data. There is little evidence of a consistent change in the endothelial function in the statin (−0.29%; 95% CI, −2.7 to 2.1 points) or the placebo (−3.6%; 95% CI, −8.4 to 1.2 points) groups; however, both groups showed a trend for improvement.

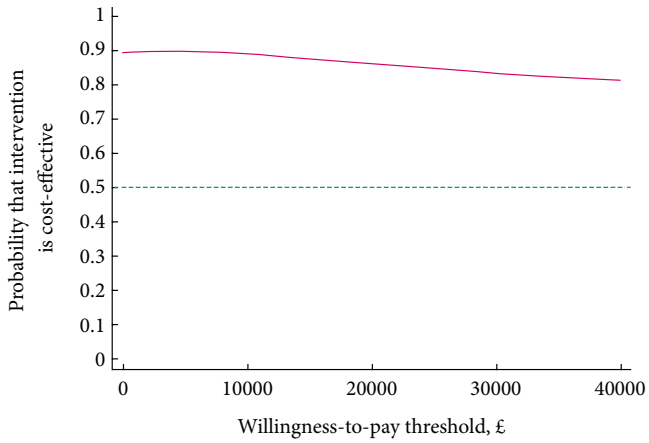
The results of the economic analysis show that, over a 24-week period, the simvastatin arm was associated with lower healthcare costs compared to placebo; however, the potential cost saving is not statistically significant (coefficient = −£68.53; $p = 0.22$) (Table 3). Similarly, after controlling for baseline utility, simvastatin is associated with small and statistically non-significant improvement in QoL (coefficient = 0.002; $p = 0.561$). The point estimate of the incremental cost-effectiveness ratio was negative and dominant. However, a negative incremental cost-effectiveness ratio is not directly interpretable. Hence, we explored the decision uncertainty around the

Table 3 Results of regression model for economic analysis.

Variable	Coefficient	Bootstrap SE	*Z*	*P* > *Z*	95% CI	
Difference in costs (£) (simvastatin – placebo)	−68.53	55.95	−1.22	0.22	−178.20	41.13
Difference in QALYs (simvastatin – placebo)	0.002	0.004	0.580	0.561	−0.006	0.011

SEs were estimated based on 10 000 bootstrap samples. QALYs, quality-adjusted life years.

Fig. 2 Cost-effectiveness acceptability curve.



cost-effectiveness of simvastatin for different WTP thresholds using the CEAC (Fig. 2). The CEAC is a method of representing the joint distribution of differences in costs and effects between intervention and control to facilitate decision-making under uncertainty. The *x*-axis in Fig. 2 shows the maximum amounts that a decision maker is able and willing to pay to achieve an additional unit of QALY gain. The *y*-axis represents the probability that simvastatin is cost-effective compared to placebo in ED patients over a 24-week period. The CEAC showed that, for the specified thresholds, the probability of simvastatin being cost-effective is high (between 0.9 at the origin to ≈0.8 at £40 000). The WTP threshold commonly used in the UK is between £20 000 and £30 000. Our analysis suggests that the probability that simvastatin is a cost-effective strategy for WTP thresholds of £20 000 and £30 000 is 0.86 (i.e. 86% chance) and 0.83 (83% chance), respectively. Hence, taking into account the uncertainty in cost and QALY benefits, there is high probability that simvastatin is cost-effective in the ED patients over 24-week period over the range of WTP thresholds.

Discussion

There was no clinically significant change in erectile function as a result of simvastatin treatment, although patients with more severe ED at baseline showed a larger change than patients with mild/moderate ED. Examination of covariates showed no confounding apparent in the data. However, simvastatin significantly improved the sexual HRQL (MED-QoL), LDL cholesterol and reduced future CVD risk. Examination of the relationship between CVD risk (of which LDL cholesterol is a component) and IIEF showed that increased CVD risk reduces the change in IIEF across the study period (5% increase in CVD risk reduces change by 0.45%). It remains unclear why the MED-QoL improved significantly with a lack of effect on the erectile function because the sexual encounter profile data showed no significant treatment effect on satisfaction or success. A number of limitations may have contributed to the observed effects. Men in the present study, as identified by questionnaire, carried a portfolio of cardiovascular risk factors that were previously unidentified and untreated. The present study excluded patients with significantly high CVD risk factors for ethical reasons. These were the men who would probably benefit from the intervention. Erectile function measured using the IIEF score defines ED principally in physical terms (i.e. hardness, penetration success), although it does not take account of wider issues related to intimate relationships, which may or may not be related to cardiovascular health. It is possible that improving cardiovascular health has more general effects on sexual health, which leads to improved sexual interactions that are not captured by the IIEF but are captured by the MED-QoL. There are also relationship issues to consider because enrolment in the present study may have altered the sexual behaviour of these couples.

The economic analysis suggests that simvastatin was associated with a reduction in healthcare costs and QALYs, although these were not statistically significant. However, the joint distribution of costs and QALYs suggests that, taking account of uncertainty in estimates, there is a high probability that simvastatin is cost-effective for WTP thresholds of £20 000–30 000. The results can be primarily attributable to reduced health service use associated with simvastatin, although this was not statistically significant. Given the reduction in cardiovascular risk and improvement in MED-QoL shown in the present study, a reduction in health services use can be expected. However, because the present study did not collect data on reasons for health service visits, it is not possible to establish whether health services were used for cardiovascular or ED-related reasons. A longer-term reduction in

cardiovascular risk probably has a further positive impact on health services resource use.

High attrition and limited concordance could have compromised the power of the present study, although the data obtained on adherence are similar to those of the SHARP (Study of Heart and Renal Protection) study of simvastatin plus ezetimibe in patients with chronic renal failure in which efficacy was reduced as a result of poor concordance [29]. There could be bias as a result of non-completion because patients completing the present study tended to be older and have a higher CVD risk than those not completing (3.1 years, $t_{171} = 2.16$, $p = 0.03$, 3.2%, $z = 2.04$, $p = 0.04$. It was noted that increasing CVD risk tended to reduce the change in IIEF across the present study. However, most commonly, patients do not complete because they do not perceive any benefit from treatment. On balance, the overall effect of these patients probably only has only a marginal influence on the observed study outcomes.

There are a number of implications of the findings of the present study with respect to practice and research. As expected, statin therapy reduced LDL significantly and, consequently, future CVD risk will be reduced in these men with ED. The mean predicted 10-year CVD risk was 12.26% in men aged 55–65 years and 23.04% in men aged >65 years, and there was a 9.6% and 14.6% reduction in future risk, respectively. Identifying men with ED provides the opportunity to modify future cardiovascular risk and improve MED-QoL by treating them with 40 mg of simvastatin.

The findings of the present study could influence primary care practice in a number of ways, such as including questions on ED during routine consultations, relevant clinic protocols (e.g. diabetes, hypertension, heart disease) and in men with lower urinary tract symptoms. Raising awareness of the links between ED and CVD provides an opportunity to provide lifestyle advice. This is further supported by data from a recent meta-analysis showing improved erectile function as a result of lifestyle intervention [30]. It has been suggested that doctors should support patient sexual activity because regular intercourse may have a positive impact on erectile function and general health and HRQL [31]. The small positive correlation between the frequency of intercourse and IIEF score found in the present study would tend to support this view.

The results of this trial, as well as the subject of ED and its identification and management, represent an important topic that is currently not optimally managed in either primary or secondary care. These could be usefully discussed at local primary care meetings supported by the Primary Care Trusts (shortly to be Clinical Commissioning Groups). Furthermore, women could be targeted to inform them about the risks associated with ED and subsequent CVD to encourage them to persuade their partners to attend for medical review. The findings of the present study may further inform the Joint British Society's revision of the guidelines on cardiovascular risk [32]. Future research could address: (i) the links between ED and CVD that require further exploration in terms of stratifying future cardiovascular risk; (ii) the need to establish whether intervening by managing risk factors in men with ED reduces future cardiovascular events; (ii) the lack of research into partner issues relating to sexual dysfunction (research nurses involved in the present study highlighted the fact that relationships appear to improve by their involvement in the study); and (iv) early data suggesting that testosterone concentrations are important in cardiovascular health and low testosterone may cause ED and therefore act as a marker [33,34]. In the present study, the total testosterone concentrations fell by 0.67 in the statin group vs 0.18 in the placebo group. Statins have been shown to reduce sex hormone-binding globulin so that free testosterone concentrations are preserved [35]. The investigation of whether testosterone concentrations are lower in men suffering from heart disease than controls is an area for future research.

The present trial has shown a significant improvement in sexual HRQL and reduced future CVD risk in men with untreated ED given 40 mg of simvastatin for 6 months. The economic analysis suggests that simvastatin for these men has a more than 80% chance of being cost-effective. Larger trials with a longer follow-up and a more potent statin are needed to establish both its effectiveness on erectile function and its cost-effectiveness.

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Conflict of Interest

Michael Kirby and Geoffrey Hackett have received funding for research, advice, lecturing and conference attendance from the Pharmaceutical Industry.

References

1 **Feldman HA, Johannes CB, Derby CA et al.** Erectile dysfunction and coronary risk factors: prospective results from the Massachusetts male aging study. *Prev Med* 2000; 30: 328–38

2 **Braun M, Wassmer G, Klotz T, Reifenrath B, Mathers M, Engelmann U.** Epidemiology of erectile dysfunction: results of the 'Cologne Male Survey'. *Int J Impot Res* 2000; 12: 305–11

3 **Laumann EO, Paik A, Rosen RC.** Sexual dysfunction in the United States. Prevalence and predictors. *JAMA* 1999; 281: 537–44

4 **Dunn KM, Croft PR, Hackett GI.** Sexual problems: a study of prevalence and need for health care in the general population. *Fam Pract* 1998; 15: 519–24

5 **Thompson IM, Tangen CM, Goodman PJ, Probstfield JL, Moinpour CM, Coltman CA.** Erectile dysfunction and subsequent cardiovascular disease. *JAMA* 2005; 294: 2996–3002

6 **Litwin MS, Nied RJ, Dhanani N.** Health-related quality of life in men with erectile dysfunction. *J Gen Intern Med* 1998; 13: 159–66

7 **Speel TGW, van Langen H, Meuleman EJH.** The risk of coronary heart disease in men with erectile dysfunction. *Eur Urol* 2003; 44: 366–71

8 **Wilson EC, McKeen ES, Scuffham PA, Brown MC, Wylie K, Hackett G.** The cost to the United Kingdom National Health Service of managing erectile dysfunction: the impact of sildenafil and prescribing restrictions. *Pharmcoeconomics* 2002; 20: 879–89

9 **British Society for Sexual Medicine.** Guidelines on the management of erectile dysfunction. 2007. Available at: http://www.bssm.org.uk/downloads/BSSM_ED_Management_Guidelines_2007.pdf. Accessed 3 February 2012

10 **Sullivan ME, Keoghane SR, Miller MAW.** Vascular risk factors and erectile dysfunction. *BJU Int* 2001; 87: 838–45

11 **Fung MM, Bettencourt R, Barrett-Connor E.** Heart disease risk factors predict erectile dysfunction 25 years later. The Rancho Bernardo Study. *J Am Coll Cardiol* 2004; 43: 1405–11

12 **Tikkanen MJ, Jackson G, Tammela T et al.** Erectile dysfunction as a risk factor for coronary heart disease: implications for prevention. *Int J Clin Pract* 2007; 61: 265–8

13 **Billups KL, Bank AJ, Padma-Nathan H, Katz S, Williams R.** Erectile dysfunction is a marker for cardiovascular disease: results of the Minority Health Institute Expert Advisory Panel. *J Sex Med* 2005; 2: 40–52

14 **Walczak MK, Lokhandwala N, Hodge MB, Guay AT.** Prevalence of cardiovascular risk factors in erectile dysfunction. *J Gend Specif Med* 2002; 5: 19–24

15 **Tsunekawa T, Hayashi T, Kano H et al.** Cerivastatin, a hydroxymethylglutaryl coenzyme a reductase inhibitor, improves endothelial function in elderly diabetic patients within 3 days. *Circulation* 2001; 104: 376–9

16 **Saltzman EA, Guay AT, Jacobson J.** Improvement in erectile dysfunction in men with organic erectile dysfunction by correlation of elevated cholesterol levels: a clinical observation. *J Urol* 2004; 172: 255–8

17 **Feldman HA, Goldstein I, Hatzichristou 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

18 **Montorsi P, Montorsi F, Schulman CC.** Is erectile dysfunction the 'tip of the iceberg' of a systemic vascular disorder? *Eur Urol* 2003; 44: 352–4

19 **Moore RA.** Sildenafil (Viagra) for male erectile dysfunction: a meta-analysis of clinical trial reports. *BMC Urol* 2002; 2: 6. doi:10.1186/1471-2490-2-6

20 **Masumoto A, Hirooka Y, Hironaga K et al.** Effect of pravastatin on endothelial function in patients with coronary artery disease (cholesterol-independent effect of pravastatin). *Am J Cardiol* 2001; 88: 1291–4

21 **Herrmann HC, Levine LA, Macaluso J Jr et al.** Can atorvastatin improve the response to sildenafil in men with erectile dysfunction not initially responsive to sildenafil? Hypothesis and Pilot Trial Results. *J Sex Med* 2006; 3: 303–8

22 **Yaman O, Akand M, Gursoy A, Erdogan MF, Anafarta K.** The effect of diabetes mellitus treatment and good glycaemic control on the erectile function in men with diabetes mellitus-induced erectile dysfunction: a pilot study. *J Sex Med* 2006; 3: 344–8

23 **Gokkaya SC, Ozden C, Levent Ozdal O, Hakan Koyuncu H, Guzel O, Memis A.** Effect of correcting

serum cholesterol levels on erectile function in patients with vasculogenic erectile dysfunction. *Scand J Urol Nephrol* 2008; 42: 437–40

24 **Trivedi D, Kirby M, Norman F, Przybytniak I, Ali S, Wellsted DM.** Can simvastatin improve erectile function and health-related quality of life in men aged > 40 years with erectile dysfunction? Rationale and design of the Erectile Dysfunction and Statins (EDS) Trial [ISRCTN66772971]. *BJU Int* 2011; 108: 1850–4

25 **Rosen RC, Cappelleri JC, Smith MD, Lipsky J, Pena 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 function. *Int J Impot Res* 1999; 11: 319–26

26 **Wagner TH, Patrick DL, McKenna SP, Froese PS.** Cross-cultural development of a quality of life measure for men with erection difficulties. *Qual Life Res* 1996; 5: 443–9

27 **Brooks R, Rabin R, de Charro F eds.** *The Measurement and Valuation of Health Status Using EQ-5D: A European Perspective: Evidence from the EuroQol BIO MED Research Programme*. Rotterdam: Kluwer Academic Publishers, 2003

28 **McEniery CM, Wallace S, Mackenzie IS et al.** Endothelial function is associated with pulse pressure, pulse wave velocity and augmentation index in healthy humans. *Hypertension* 2006; 48: 602–8

29 **Baigent C, Landray MJ, Reith C et al.** SHARP collaborators). The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* 2011; 377: 2181–92

30 **Gupta BP, Murad H, Clifton M, Prokop L, Nehra A, Kopecky SL.** The effect of lifestyle modification and cardiovascular risk factor reduction on erectile dysfunction. A systematic review and meta-analysis. *Arch Intern Med* 2011; 171: 1797–803

31 **Koskimaki J, Shiri R, Tammela T, Häkkinen J, Hakama M, Auvinen A.** Regular intercourse protects against erectile dysfunction: Tampere Aging Male Urologic Study. *Am J Med* 2008; 121: 592–6

32 JBS2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart* 2005; 91 (Suppl. 5): V1–52

33 **Shores MM, Matsumoto AM, Sloan KL, Kivlahan DR.** Low serum testosterone and mortality in male veterans. *Arch Intern Med* 2006; 166: 1660–5

34 **Khaw KT, Dowsett M, Folkerd E et al.** Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European prospective investigation into cancer in Norfolk (EPIC-Norfolk) Prospective Population Study. *Circulation* 2007; 116: 2694–701

35 **Stanworth RD, Kapoor D, Channer KS, Hugh Jones T.** Statin therapy is associated with lower total but not bioavailable or free testosterone in men with type 2 diabetes. *Diabetes Care* 2009; 32: 541–6

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Abbreviations: CEAC, cost-effectiveness acceptability curve; CVD, cardiovascular disease; HRQL, health-related quality of life; IIEF, International Index of Erectile Function; LDL, low-density lipoprotein; MED-QoL, male erectile dysfunction-specific quality of life; QALY, quality-adjusted life years; SEP, sexual encounter profile; WTP, willingness-to-pay.

Supporting Information

Additional supporting information may be found in the online version of this article:

Video.

