The temporal relationship between erectile dysfunction and cardiovascular disease

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SUMMARY
Background: Erectile dysfunction (ED) and cardiovascular disease (CVD) share similar risk factors, and ED may be a marker of CVD progression. The study assessed: (i) the temporal relationship between ED and CVD and (ii) the UK incidence of ED, in patients with CVD and an age-matched control group. Design: After ethics approval, 207 patients (CVD group) attending cardiovascular rehabilitation programmes and 165 age-matched subjects (control group), from GP practices across the UK, completed up to four questionnaires (ED details, The International Index of Erectile Function (IIEF) (before and after a cardiovascular event) and ED related Quality of Life). A health professional also completed a medical details questionnaire. Results: Erectile dysfunction was reported by 66% of individuals with CVD, with a mean duration of 5 ± 5.3 years. The control group was significantly different (p < 0.05) in both incidence (37%) and mean duration (6.6 ± 6.8 years). Only 53% of the CVD group and 43% of the control group had discussed their symptoms of ED with a health professional. The IIEF demonstrated that ED became significantly worse (p < 0.05) after a cardiovascular event, changing from moderate to severe (13–10). Conclusions: From these data, it is now evident that ED may precede a cardiovascular event by as much as 5 years. In almost half of the men with ED, there were missed opportunities to undertake a CVD risk assessment and provide an intervention, because the men did not acknowledge the problem. Men with ED should be specifically targeted for CVD preventative strategies in terms of lifestyle changes, and appropriate pharmacological treatments.

Introduction
Erectile dysfunction (ED) is defined as the persistent inability to attain and maintain an erection sufficient for sexual performance (1). A greater awareness of the mechanisms of ED has developed as a result of increased awareness. Vascular diseases have been documented as the most common cause of ED and thus share similar aetiologies and pathophysiology (e.g. endothelial dysfunction), including age, smoking, diabetes, heart disease, depression and hypertension (2,3).

Cardiovascular disease (CVD) is the leading cause of mortality in the UK accounting for more than 39% of deaths per annum (4). In 1994, the Massachusetts Male Aging Study (MMAS) (5) identified a prevalence of ED in 52% of men aged between 40 and 70 years and 70% of men aged > 70 years of age. The study also demonstrated an initial association between ED and CVD, which has been subsequently confirmed in large epidemiological studies, in many countries (6–9). In 1997, Greenstein et al. (10) showed evidence that the degree of ED was correlated with the severity of CVD and in 1999, Pritzker demonstrated abnormal exercise ECGs in 28 of 50 asymptomatic men (other than ED). Pritzker also identified severe coronary artery disease (CAD) in six men, moderate two vessel disease in seven men and single vessel disease in a further seven men (11). In a study of 132 men attending day case angiography, 40% had experienced ED before CAD diagnosis (12). In 2003, Montorsi et al. proposed that the arteries in the penis would suffer obstruction from plaque earlier than the coronary or carotid arteries because the diameter of the arteries in the penis were smaller (1–2 mm) compared with the coronary (3–4 mm) or carotid arteries (5–7 mm), hence ED would be symptomatic before a cardiovascular event (13,14). The
Princeton II guidelines highlight the importance of ED as a marker for CVD in men with no previous symptoms (15–17), and that symptoms of ED may be the first visible sign of endothelial dysfunction (18,19). A recent review, not only stresses the importance of detecting ED but of screening individuals who do have ED for other undiagnosed cardiovascular-related diseases (20).

As outlined in the National Service Framework for Coronary Heart Disease, early identification of people at risk of CVD is vital for effective management of the condition (21). There is consensus that individuals with ED should be investigated for cardiovascular risk factors and targeted for cardiovascular preventative strategies (22–24). The Second Princeton II consensus guidelines recommend that all men with ED should undergo a full medical assessment (25). However before this, it is paramount that we discover the timeframe between onset of ED and progression to a significant cardiovascular event in which early identification and treatment of ED may improve an individual’s prognosis concerning a cardiovascular event.

This study was undertaken with the primary aim of further exploring the temporal relationship between ED and CVD and with the secondary aim of determining the UK prevalence of ED amongst individuals with CVD and an age-matched control group.

Materials and methods

The study was a quasi cross-sectional, questionnaire-based, age and geographically matched, two group design (patients with CVD vs. patients without CVD) powered to establish group differences in ED.

After Ethics and Research and Development approval, 207 men with CVD were recruited from 15 Cardiac Rehabilitation Centres and 165 age and geographically matched subjects (control), without diagnosed CVD, were recruited from 16 GP Practices throughout the UK. Individuals in the cardiovascular group were included if they presented with myocardial infarction (MI); stroke; transient ischaemic attack; attended a rapid chest pain clinic and received a positive diagnosis for CVD; angina or claudication. However, cardiovascular risk factors such as hyperlipidaemia and high blood pressure were not an exclusion. All the above exclusion criteria also applied to the control group.

Each subject was sent a coded invitation pack. To maintain anonymity of subjects, invitation packs were coded and mailed to the subjects from the Cardiac Rehabilitation Centres and GP Practices. Each pack contained an invitation letter from the Cardiac Rehabilitation Centre or GP Practice, an invitation letter from Buckinghamshire Chilterns University College, a patient information sheet, two informed consent forms, a leaflet providing information on medical research and a prepaid envelope. The prepaid envelope contained an instruction sheet, Questionnaire 1 (Erectile Dysfunction Details), Questionnaire 2 [five-item International Index of Erectile Function (IIEF) before a cardiovascular event], Questionnaire 3 (five-item IIEF after a cardiovascular event) and Questionnaire 4 [ED-Quality of Life (QoL)]. The control group only had one five-item IIEF questionnaire to complete. The questionnaires were returned to the research centre, where a questionnaire relating to patient details was sent to the relevant GP Practice or the Cardiac Rehabilitation Centre to complete.

The IIEF, an internationally accepted standard for defining sexual function, assesses four domains with a 15-item questionnaire (26,27). The IIEF-5 questionnaire is an abbreviated form of the IIEF, with four items selected from the erectile domain portion of the IIEF and one item addressing sexual satisfaction (28). The IIEF has been validated (28,29) and correlated with patient reports of ED (29). The erectile function domain score is calculated from the sum of questions 1–4 for men with complete answers to the IIEF. The degree of ED, is classified as, complete (≤ 4), severe (5–10), moderate (11–15), mild (16–20) or none (21–25) (28,30). The IIEF-5 has not been validated to be used retrospectively and this is recognised as a limitation to the study.

The ED-QoL Questionnaire is a robust instrument measuring the impact of ED on QoL. It is simple to complete and fulfils the usual psychometric properties of reliability, validity and responsiveness (31). The ED-QoL score is calculated as the sum of 15 questions (a score of 30 or more implies that the individual answered ‘quite a lot’ to at least one
question). A score of < 15 indicates the individual’s QoL is not or only mildly affected by ED, a score of 15–29 indicates that an individual’s QoL is moderately affected and a score of 30 or more may indicate that an individual is severely affected.

Results

Table 1 shows clinical characteristics of the CVD group and the control group. This illustrates that there was little difference between the groups, with the exception of total cholesterol and low-density lipoprotein cholesterol which were slightly higher in the control group than in the CVD group. This may be due to the fact that the CVD group were on medication for cholesterol (see Table 2) and therefore it was well controlled.

### CVD group

The data demonstrate that 66% of individuals with CVD have experienced ED and 56% of individuals were currently suffering from ED. These individuals had been experiencing ED symptoms for a mean of 5 ± 5.3 years and only half had discussed their problem with a health professional. Table 3 shows the length of time individuals have suffered with ED. From the table it is possible to state that in 50% of the men with ED, the problem has lasted 3 years or less and in 73% has been evident for 6 years or less. Table 3 also allows for a simple comparison between length of suffering from ED between individuals who have had a cardiovascular event and those who have not. One can observe that the control group mirrors that of the CVD group in the percentages of individuals and how long they have had ED. Fifty-seven per cent of individuals, who reported symptoms of ED, were not experiencing nocturnal erections. After individuals had suffered a cardiovascular event, 69% of those who had initially reported ED to a health professional, reported their symptoms again. This is important because it demonstrates that a cardiovascular event provides the opportunity to discuss ED with a health professional, a situation that rarely occurs. A further 11%, who had not previously discussed their ED problem, did so, with a health professional after their cardiovascular event.

The data from the IIEF-5 questionnaire completed by patients as if before their cardiovascular event demonstrated ED in 55% (mild = 15.5%, moderate = 14.5% and severe = 15%). A further 16% went on to develop ED (IIEF-5 score < 20) after they had suffered a cardiovascular event (Table 4). Thirty-five per cent of subjects reported a worsening of their ED following their cardiovascular event. A significant difference (p < 0.05) in the IIEF-5 scores reported before (13 ± 6) and after (10 ± 7) the CVD events was established, when ED score moved from moderate to severe (Table 4). The percentage of the control group with moderate ED was less than the CVD group prior to a CVD event, but only 43% of those with ED had discussed the issue with a health professional. Only 15% of the CVD group were currently receiving treatment.

### Controls

Within the control group, 43% of individuals reported ED, with 37% of individuals currently suffering with ED for a mean of 6.6 ± 6.8 years. Fifty-two per cent of ED sufferers had lost nocturnal or early morning erections and only 43% have had a discussion with a health professional. Only 8% of those with ED are receiving treatment.

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**Table 1 Clinical characteristics of each group**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cardiovascular disease group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61 ± 8</td>
<td>61 ± 9</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.73 ± 0.07</td>
<td>1.73 ± 0.06</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>86 ± 15</td>
<td>80 ± 12</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>4.3 ± 1.18</td>
<td>5.34 ± 1.14</td>
</tr>
<tr>
<td>HDL</td>
<td>1.23 ± 0.48</td>
<td>1.45 ± 0.44</td>
</tr>
<tr>
<td>LDL</td>
<td>2.42 ± 0.98</td>
<td>3.19 ± 1.02</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>1.56 ± 0.76</td>
<td>1.48 ± 0.86</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>130 ± 19</td>
<td>134 ± 15</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>78 ± 11</td>
<td>79 ± 8</td>
</tr>
</tbody>
</table>

HDL, high-density lipoprotein; LDL, low-density lipoprotein; BP, blood pressure.

**Table 2 Medication for the cardiovascular disease group**

<table>
<thead>
<tr>
<th>Medication</th>
<th>ED (%)</th>
<th>No ED (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>91</td>
<td>97</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>31</td>
<td>43</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>80</td>
<td>77</td>
</tr>
<tr>
<td>Ace inhibitors</td>
<td>69</td>
<td>57</td>
</tr>
<tr>
<td>Alpha blockers</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>Angiotensin II receptor blockers</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Diuretics</td>
<td>29</td>
<td>15</td>
</tr>
<tr>
<td>Nitrates</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Potassium channel activators</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Lipid-lowering drugs</td>
<td>91</td>
<td>94</td>
</tr>
</tbody>
</table>

ED, erectile dysfunction.
In those men with ED, QoL scores were similar in the CVD group (22 ± 16) and the control group (22 ± 14), demonstrating that individuals’ QoL were moderately affected by their ED. MacDonagh et al. (32) showed higher QoL scores in individuals with ED (27.6 ± 14.2) when validating the ED-QoL questionnaire.

Discussion

Although the link between ED and CVD has been previously documented, there is much interest regarding the temporal relationship. This study provided an opportunity to assess the relationship between the timing of ED and CVD.

In this study the incidence of ED prior to (66%) and after (79%) a cardiovascular event was higher than amongst the controls (43%). These data are similar to that identified in other studies involving CVD patients where incidence rates have been shown to vary between 34% and 70% depending on diagnostic criteria (5,12,33,34). This study demonstrates the increased incidence of ED prior to any substantial cardiovascular event indicating that it may be a precursor to a cardiovascular event and that it is likely to become significantly worse afterwards.

The high incidence of ED following a cardiovascular event is likely to be multifactorial. This may be caused by physiological, psychological, iatrogenic or a combination of these factors (35). After a cardiovascular event 43% of individuals reported having early morning and nocturnal erections. It is therefore possible that some of the cases still getting these erections in the present study may have psychogenic ED as an additive component. The significant incidence of ED, demonstrates the importance of asking men about erectile function after a cardiovascular event and discussing appropriate treatment options (23).

It is recommended to re-assess sexual function during a 6-month time interval. However, by this time most post-MI patients will have moved on to phase IV cardiac rehabilitation where the opportunities for such discussion will be limited. It is therefore imperative that issues concerning ED are debated during phase II and III cardiac rehabilitation.

The concept that a man with ED and no cardiac symptoms, is a cardiac (or vascular) patient until proved otherwise, has developed with the recognition of ED as an early warning sign of silent vascular disease (25,36–39). The Princeton II consensus guidelines recommend that all men with ED should undergo a full medical assessment (Figure 1), with the establishment of cardiovascular risk graded low, moderate or high. Roumeguere et al. (40) demonstrated that the prevalence of individuals with hyperlipidaemia was 70% in individuals with ED, and the increased 10-year coronary heart disease risk was found in 56% of the ED group compared with 32.6% of the control group. In the current study 10-year cardiac risk was assessed in the apparently ‘healthy subjects’ who reported ED. Based on the Joint British Societies’ CVD risk prediction chart (36), 50% of the controls that presented with ED had a moderate-to-high 10-year risk. It was also noted, that since completing the questionnaires one of the controls who had ED went on to suffer a significant cardiovascular event which could possibly have been prevented through appropriate treatment. This highlights the importance of completing a cardiovascular risk assessment on all individuals who

### Table 3 Duration of ED before cardiovascular event compared with controls

<table>
<thead>
<tr>
<th>Duration of ED (years)</th>
<th>Percentage CVD</th>
<th>Cumulative percentage</th>
<th>Percentage control</th>
<th>Cumulative percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1</td>
<td>14</td>
<td>14</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>1–3</td>
<td>35</td>
<td>49</td>
<td>34</td>
<td>47</td>
</tr>
<tr>
<td>4–6</td>
<td>24</td>
<td>73</td>
<td>24</td>
<td>71</td>
</tr>
<tr>
<td>7–10</td>
<td>17</td>
<td>90</td>
<td>13</td>
<td>84</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>10</td>
<td>100</td>
<td>16</td>
<td>100</td>
</tr>
</tbody>
</table>

ED, erectile dysfunction; CVD, cardiovascular disease.

### Table 4 Degree classification of ED severity

<table>
<thead>
<tr>
<th>ED severity</th>
<th>IIEF-5 before CVD (%)</th>
<th>IIEF-5 after CVD (%)</th>
<th>Control IIEF-5 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete ≤ 4</td>
<td>10</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>Severe 5–10</td>
<td>15</td>
<td>26</td>
<td>9</td>
</tr>
<tr>
<td>Moderate 11–15</td>
<td>14.5</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>Mild 16–20</td>
<td>15.5</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>None 21–25</td>
<td>45</td>
<td>29</td>
<td>56</td>
</tr>
</tbody>
</table>

ED, erectile dysfunction; CVD, cardiovascular disease; IIEF, International Index of Erectile Function.
present with ED and demonstrates that all individuals should be investigated for vascular disease until proven otherwise.

Data reported by Thompson et al. (38), demonstrated that 1 year after initial report of ED, 2% of the men had experienced an initial cardiovascular event while by 5 years, 11% had had cardiovascular events. A recent study by Stroberg et al. (34) reported three-quarters of the men with MI had had ED for 3 years before. Montorsi et al. (41) reported that from 300 consecutive patients with acute chest pain and angiographically documented CAD, 49% had ED and had done so for a mean of 3 years. They also documented that ED may be evident prior to angina symptoms in almost 70% of cases. Montorsi et al. (42) also demonstrated that ED comes before CAD in the majority by an average of 2–3 years and is greater in individuals with more severe CAD. The current study similarly demonstrates a possible 3-year window of opportunity, in which significant lifestyle modifications and drug therapy could be initiated for preservation of cardiovascular health. Physicians and nurses should undertake a cardiovascular risk assessment on all individuals who present with ED. Based on the current data there is evidence of ED as an important marker for future development of cardiovascular events.

The current study demonstrated an increase in the number of individuals with severe and complete ED prior to (15% and 10% respectively) and after a cardiovascular event (18% and 26% respectively). This was consistent with the MMAS, where it was demonstrated that individuals with cardiac disease had a 39% chance of complete ED (5). The significant increase in the severity and the number of individuals suffering with moderate and severe ED demonstrates how important it is for the clinician to ask about ED when a patient is diagnosed with CVD.

An important objective of cardiac rehabilitation is the restoration of adequate sexual function and satisfaction, yet this is reported to be frequently omitted from cardiac rehabilitation programmes (43). This study demonstrates that cardiac rehabilitation staff are only occasionally asking individuals about ED and that the patients themselves are not reporting their ED for a variety of reasons (44,45,22). In view of the prevalence in this population and its impact, ED should be asked about routinely and sensitively (22). A treatment strategy for cardiovascular diagnostic evaluation and preventative treatment has been described by Jackson et al. (22), for individuals who present with ED. All currently licensed ED treatments are suitable for managing ED in the cardiovascular patient according to the manufacturer’s instructions, with the exception of patients on warfarin who may experience increased risk of bruising with injections, urethral bleeding with intra-urethral alprostadil and haematoma with the vacuum device and patients taking nitrate therapy or nicorandil in whom sildenafil is contraindicated and apomorphine is cautioned.

Clinicians play an important role in the early detection of ED which provides an opportunity to request further investigations and perform specific diagnostic evaluations for CVD. However, the presence of ED will only be a useful prompt for

Figure 1 Princeton II evaluation algorithm (17)
subsequent preventative treatment if either the individual reports it to a health professional or the health professional enquires specifically about the condition. Our evidence shows that in half of the ED cases, there are missed opportunities to undertake a risk assessment and provide an intervention. Men with ED should be specifically targeted for CVD prevention strategies both pharmacologically and in terms of lifestyle changes.

Limitations

It is well known that recall reliability can be affected by several biases. Recall bias may affect the reliability and may compromise the validity of such data. Statistically significant errors have been reported in several disease processes (46–49). Sources of error may relate to the difficulty of the questions, or to the recall process required to access the desired information from memory. In urological studies it has been shown that recalled impressions of sexual function has exceeded prospectively assessed function when recall ranged from 7 to 37 months (46). When the recall time was 6 months, strong to reasonable agreement was found (50). Karakiewicz et al. (51) tested the reliability of the IIEF domain scores before, 6 and 12 months after radical prostatectomy. The erectile function domain, which contributes the greatest recall reliability intraclass correlation coefficient 0.65–0.73. Therefore we can conclude that the IIEF-5 used in the present study has sufficient reliability to be used as a recall tool within this population.

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References

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