The increasing role of PDE5Is in men with diabetes and cardiovascular disease

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Diabetes is strongly associated with erectile dysfunction, which is itself a risk factor for cardiovascular events and mortality. Evidence shows that phosphodiesterase type 5 inhibitor (PDE5I) use in men with type 2 diabetes mellitus is associated with a significant reduction in all-cause mortality and morbidity. Despite the evidence, PDE5Is appear to be underused in this male cohort.

Type 2 diabetes mellitus (T2DM) is a major health and economic concern for the western world and is more common in men. In the UK in 2018, 26% of the population over 65 years of age had been diagnosed and 56% of these were men. The prevalence is six times greater in men of South East Asian origin and three times greater in African-Caribbean men.[1] In the USA, two-thirds of men over 65 years old have T2DM and 1 in 3 are living with prediabetes, 84% of whom are unaware.[2] Mortality in T2DM is 32% higher, with mean life expectancy reduced by six years when the diagnosis is made in men over 50.

The UK prospective diabetes study (UKPDS) confirmed that each increase of 1% in HbA_{1c} increases the risk of diabetes-related death by 21%, myocardial infarction by 14% and peripheral vascular disease by 43%.[3] Currently, men diagnosed with T2DM over age 40 years should be routinely started on metformin, statin and ACE inhibitor or angiotensin receptor blocker, as preventative strategies, according to NICE guidance.[4]

T2DM is strongly associated with erectile dysfunction, which contributes to poor quality of life. A recent study was designed to determine the prevalence of erectile dysfunction and its predictors among men with T2DM. The hospital-based cross-sectional observational study was conducted at a tertiary care centre and included 357 men with T2DM recruited over 18 months. Erectile dysfunction was identified using the International Index of Erectile Function (IIEF) score and was found in 59.38% of the men. There was a strong negative correlation between IIEF score and age (r= –0.647), and a moderate negative correlation with duration of T2DM (r= –0.324), systolic blood pressure and diastolic blood pressure. BMI, fasting blood sugar, serum cholesterol and serum creatinine also showed a weak negative correlation with IIEF score. Serum testosterone level showed a strong positive correlation with IIEF. Age, systolic blood pressure, duration of diabetes, fasting blood sugar and serum-free testosterone (p<0.05) were independent predictors of erectile dysfunction.[5]

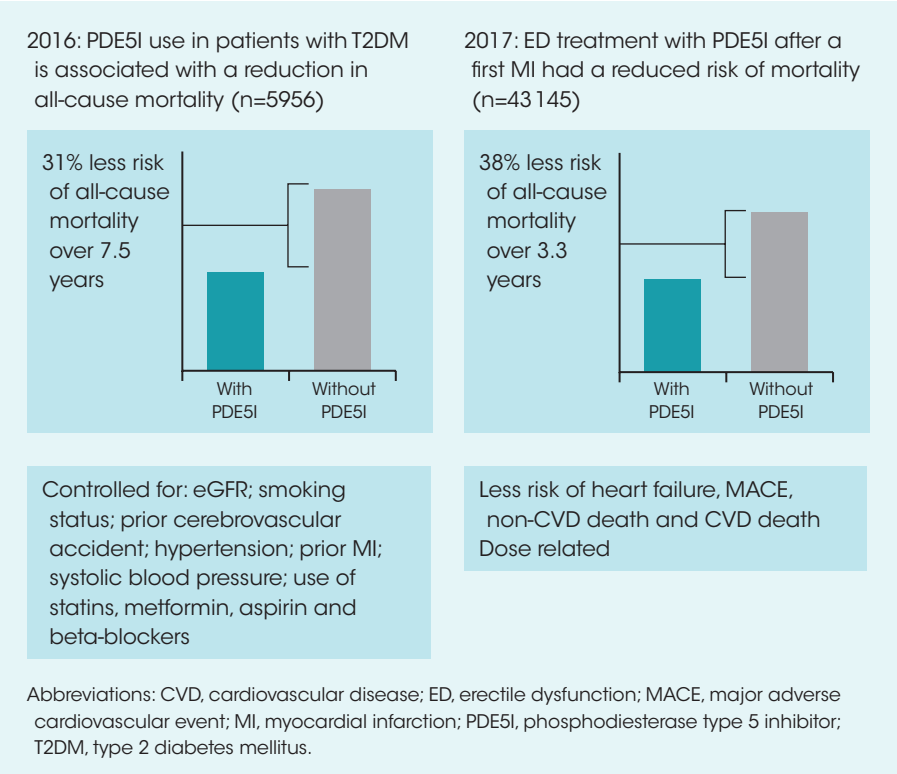

Figure 1. Mortality benefits of phosphodiesterase type 5 inhibitor treatment in patients with type 2 diabetes and those with erectile dysfunction[10,12]

Erectile dysfunction: an independent risk factor

Erectile dysfunction is acknowledged as an independent risk factor for cardiovascular events and mortality, and is now included in risk calculators.[6,7] PDE5Is are first-line agents in treatment for erectile dysfunction, and importantly, longitudinal studies suggest that PDE5Is reduce all-cause mortality in men with T2DM, previous myocardial infarction, erectile dysfunction (Figure 1) and benign prostatic hypertrophy (BPH). A review of PDE5Is and all-cause mortality (excluding pulmonary hypertension and heart failure) identified five recent studies.[8,9–12] These studies show a significant reduction in all-cause mortality and morbidity associated with PDE5I use in men with T2DM, the general population and men with lower urinary tract symptoms (LUTS).

The two most recent studies underscore the potential cardiovascular benefits. Kloner *et al.* demonstrated the effect of PDE5Is on major adverse cardiovascular events and overall mortality in a large nationwide cohort of men with erectile dysfunction and cardiovascular risk factors (Figures 2 and 3). The research was from a US database of 48692 men, reporting a 25% reduction in overall mortality after three years, but a 55% reduction in major adverse cardiovascular events (MACE) and 41% reduction in all-cause mortality in high cardiovascular risk patients, with dose-related response. The highest exposures to PDE5Is were also associated with significantly greater reductions in myocardial infarction and stroke compared with lower exposures. In a subgroup of men with erectile dysfunction and cardiovascular risk factors, Kloner *et al.* observed a 13% lower incidence of MACE, 25% reduction in all-cause mortality and 39% reduction in cardiovascular mortality, in those exposed to PDE5I medications. The authors called for urgent studies to assess risk reduction in randomised controlled trials.[8]

Despite these findings, prescribing of PDE5Is is often avoided in higher risk patients and dosing is still often restricted to one tablet on-demand per week.

Tadalafil has been associated with decreased risk of MACE or venous thromboembolism in men with LUTS. In the second study, Goberdhan *et al.* investigated 851 492 men with BPH treated with alpha blocker versus daily tadalafil and reported a 43% reduction in MACE/thrombotic events over three years with daily tadalafil.[9]

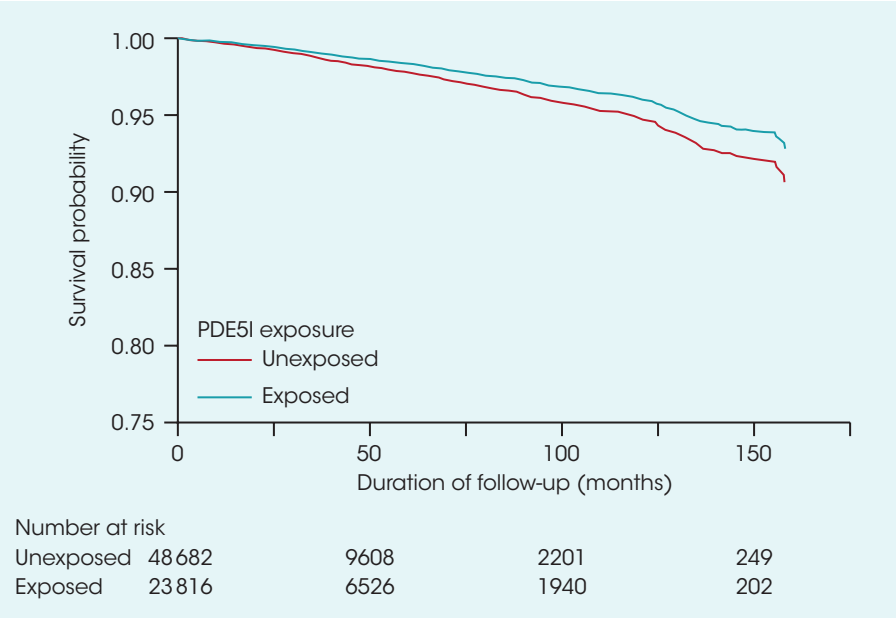

Figure 2. Adjusted survival curves showing the effect on overall mortality in men with erectile dysfunction treated with phosphodiesterase type 5 inhibitor (PDE5I) compared with controls not treated with PDE5I[8]

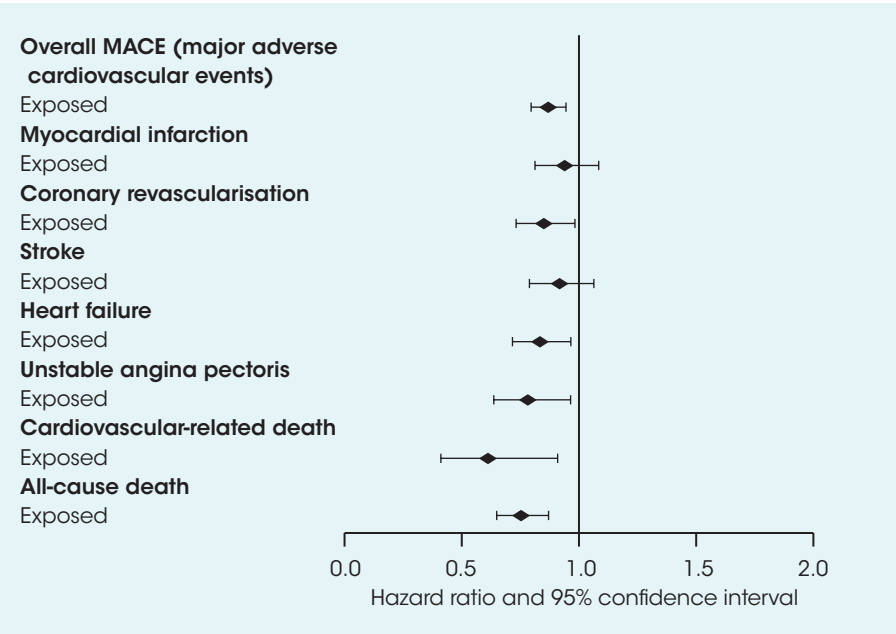

Figure 3. Forest plot (matched and adjusted hazard ratios) showing impact on cardiovascular events in men with erectile dysfunction of treatment with phosphodiesterase type 5 inhibitor (PDE5I) compared with controls not treated with PDE5I[8]

Guidance on LUTS and BPH

Men with T2DM have a 32% higher prevalence of LUTS/BPH due to shared mechanisms of chronic inflammation, insulin resistance, endothelial dysfunction, pelvic atherosclerosis and sympathetic overactivity (Box 1).[13] But first-line NICE advice for men with minimal prostate enlargement is an alpha blocker,[14] known to adversely affect ejaculation, which may already be affected by autonomic neuropathy in men with T2DM.[4] In addition,

Box 1. Erectile dysfunction in type 2 diabetes mellitus

Related to duration, control and number of complications of diabetes:

- Autonomic neuropathy
- Peripheral neuropathy
- Hypertension
- Peripheral vascular disease
- Dyslipidaemia
- Drug side-effects
- Benign prostatic hyperplasia (lower urinary tract symptoms)
- Depression
- Hypogonadism (double risk)
- Psychological factors
- Ejaculatory disorders: retrograde/anejaculation
- Reduced sensation

co-prescribing an on-demand PDE5I with an alpha blocker is more likely to produce symptomatic hypotensive episodes in men with T2DM[15] due to comorbid autonomic neuropathy, co-prescribed antihypertensives and hypoglycaemia. Recent evidence suggests that alpha blockers may precipitate heart failure.[16]

European Association of Urology (EAU)[17] and British Society for Sexual Medicine (BSSM)[18] guidelines recommend daily tadalafil as first-line for men with erectile dysfunction and LUTS, but unfortunately this strategy is not advised by NICE, nor are diabetes specialists likely to follow urology or sexual medicine guidelines.

Likewise, American Urological Association (AUA),[19] American Diabetes Association (ADA),[20] American Association of Clinical Endocrinologists (AACE)[21] and BSSM[22] guidelines all recommend testosterone measurement in men with T2DM, with or without ED, but testosterone is not considered in current NICE guidance on T2DM and there is no NICE guidance on erectile dysfunction, even after 22 years of PDE5Is.

The case for daily tadalafil

Modern cardiovascular risk strategies revolve around reducing the impact of the modifiable risk factors as demonstrated in the INTERHEART study.[23] It is therefore logical that erectile dysfunction should be approached in the same fashion as other independent risk factors. The chronic pathological process is endothelial dysfunction, and this has been shown to be modified by use of PDE5Is in many studies.

Rosano *et al.* demonstrated significant improvement in endothelial function after two weeks, which persisted two weeks after treatment cessation.[24]

Amano *et al.* investigated 81 men with ED and LUTS treated with tadalafil 5mg daily for 12 months and found significant improvements in IIEF at three months (continuing improvement at 12 months), IPSS after one month, brachial-ankle pulse wave velocity and ankle-brachial index after three months.[25]

Ramirez *et al.* demonstrated that daily dosing with sildenafil improved insulin sensitivity in men with prediabetes.[26]

Santi *et al.* investigated 54 men with T2DM in a 24-week placebo-controlled study of vardenafil 10mg twice daily and found significant improvements in IIEF, flow-mediated dilatation, IL-6 and testosterone levels in the cohort with hypogonadism.[27]

Aversa *et al.* investigated 45 men with erectile dysfunction treated with either 5mg tadalafil daily or 20mg on demand and found that only daily tadalafil improved flow-mediated dilatation, insulin sensitivity and lean muscle mass.[28]

Santi *et al.* conducted a meta-analysis of 12 RCTs (n=476) involving chronic PDE5Is in T2DM and concluded clear evidence of improved flow-mediated dilatation and reduction of IL-6 , with high-sensitivity C-reactive protein (hs-CRP) improvement just failing to reach statistical significance. Selected studies involved sildenafil (25–100mg daily), usually for 12-week maximum duration.[29]

Lee *et al.* conducted a 12-week study of tadalafil 5mg daily in men with T2DM and found that severity of erectile dysfunction was related to baseline hs-CRP. Erectile dysfunction response rate based on SEP 3 was 70%. Median hs-CRP levels were 0.31mg/dl (range 0.18–0.62mg/dl) in non-responders and 0.14mg/dl (range 0.09–0.4mg/dl) in responders, respectively (p=0.028).[30]

Schwartz *et al.* reviewed studies of tadalafil 5mg daily on endothelial function and suggested that these effects might translate into a long-term reduction in cardiovascular risk.[31]

Daily tadalafil effects on testosterone levels

Men with T2DM have low levels of testosterone in up to 40% with associated cardiovascular risk.[2] Many may be candidates for testosterone therapy to improve sexual symptoms, quality of life and cardiovascular risk. Hellstrom *et al.*, in a placebo-controlled study designed to assess sperm parameters in 253 men treated with tadalafil 20mg daily for three months, found significant increases in total testosterone versus placebo and no significant effect on semen parameters over three cycles.[32]

Oscan *et al.* treated 40 men who had metabolic syndrome with tadalafil 5mg for three months with an increase of testosterone from 11.45nmol/L (baseline) to 16.5nmol/L, and IIEF-5 from 11.3 to 19.[33] The authors recommend tadalafil 5mg once daily in those men with erectile dysfunction, especially with low testosterone levels accompanied by metabolic syndrome.

Spitzer *et al.* treated 106 men with sildenafil 50–100mg for 3–7 weeks (mean 2.6 doses on demand per week) and found a mean rise in testosterone of 3.6nmol/L and corresponding fall in LH. The authors suggested that the beneficial effect on androgen levels might be related to a direct effect of testicular blood flow rather than increased sexual activity.[34]

These studies suggest a possible beneficial effect on androgen levels if there is a wish for testosterone therapy to be avoided or as an adjunct to testosterone treatment.

PDE5Is and cardiovascular-related morbidity and mortality

PDE5Is were developed as daily therapy to treat cardiovascular disease and improvements in erectile dysfunction

were an incidental finding during clinical trials. Sildenafil and tadalafil are licensed to treat pulmonary hypertension through their beneficial effects on endothelial dysfunction.[4]

Several cardiology reviews have highlighted the beneficial mechanisms that would potentially reduce cardiovascular events in high-risk populations such as men with T2DM.[35] These include improved endothelial function, enhanced cGMP and cAMP activity to counterbalance hypertrophic and pro-apoptotic signalling, and enhanced post-ischaemic reperfusion. *In vitro* experiments suggest likely benefits in patients with heart failure.[36] Currently tadalafil 5mg is the only PDE5I licensed for daily use.

Anderson *et al.* followed a UK primary care population of 5956 UK men with T2DM over 6.9 years. A 31% reduction in all-cause mortality and 26% reduction in myocardial infarction were reported in men taking PDE5Is. Only 22.8% of men with T2DM had been prescribed a PDE5I, with patients usually restricted to taking their medication once per week.[10] These findings were supported by Hackett *et al.* in a prospective RCT of testosterone therapy in T2DM. The 175 men taking PDE5Is showed a significant and independent reduction in all-cause mortality.[11]

Andersson *et al.* reported data from a Swedish database of 43415 men after first myocardial infarction and found significant five-year reduction in all-cause and cardiovascular mortality, and 30% reduction in new diagnosis in heart failure and related admissions, among men prescribed PDE5Is. The benefits were greater in men on more frequent dosing of PDE5Is and were not seen with other therapies for erectile dysfunction.[36]

Scranton *et al.* carried out a complex health care review and concluded that diagnosis and successful treatment of concomitant erectile dysfunction may promote improved adherence and management of comorbid diseases whilst decreasing health care costs and deterioration in comorbid medical conditions.[37]

Prevention of diabetic peripheral neuropathy

Diabetic peripheral neuropathy occurs in approximately 30% of men with T2DM and currently the mainstay of prevention is through tight glycaemic control. There are numerous case reports of improvement in neuropathic pain and paraesthesia with PDE5Is.[38,39] Nitric oxide is the major neurotransmitter of the vasa nervorum, suggesting an important preventative role in microvascular complications. Currently, drugs used to treat established diabetic peripheral neuropathy effectively block pain pathways and frequently aggravate erectile dysfunction. There is huge potential for savings by the prevention of complications of diabetic peripheral neuropathy.[38,39]

Box 2. Beneficial effects of phosphodiesterase type 5 inhibitors

- Significant reduction in all-cause mortality and morbidity in men with type 2 diabetes mellitus:
  - 25% reduction in overall mortality after three years
  - 55% reduction in major adverse cardiac events
  - 41% reduction in all-cause mortality in high-risk cardiovascular patients, with dose-related response
  - Reduction in all-cause mortality in men with previous myocardial infarction, erectile dysfunction and benign prostatic hypertrophy
  - Improvement in neuropathic pain and paraesthesia in diabetic neuropathy
- EAU and BSSM guidelines recommend daily tadalafil as first-line for men with erectile dysfunction and lower urinary tract symptoms
  - Decreased risk of major adverse cardiovascular events or venous thromboembolism in men with lower urinary tract symptoms
  - Beneficial effect on serum testosterone levels
- Management of pulmonary hypertension through the beneficial effects on endothelial dysfunction
- Reduction in pulmonary hypertension, acute inflammation and endothelial dysfunction in severe COVID-19 infection

Vasculitis in severe COVID-19 infection

Several papers have suggested an important role of daily PDE5Is in acute COVID due to beneficial effects on pulmonary hypertension, acute inflammation and endothelial dysfunction.[40,41] A recent double-blind placebo-controlled study of seven days of sildenafil in acutely ill patients with COVID-19 found five-fold decreased mortality and halving in ITU admissions in the PDE5I group, suggesting an important role in acute COVID infection and a need for further studies.[42]

Conclusions

Prescribing policies for T2DM are largely decided by diabetes specialists, with priorities given to glycaemic control. Comorbid conditions such as erectile dysfunction and BPH are usually managed by urologists. The recognition of erectile dysfunction as an independent risk factor for coronary heart disease justifies inclusion in routine risk reduction strategies. Guidelines often suggest 'consider measuring testosterone if clinically indicated', but sexual histories are still not taken in routine diabetes practice. As erectile dysfunction affects over 75% and hypogonadism over 40%, accurate assessment of both these issues should be mandatory in routine diabetes care. Evidence that PDE5Is produce benefits through multiple mechanisms (Box 2), including a rise in testosterone level (with daily medication), now supports routine prescribing of these agents on a daily basis in diabetes care, not least because the patients will potentially experience symptomatic improvements that will increase compliance with other prescribed interventions. Earlier NICE guidance on daily dosing with tadalafil for its licensed indications of erectile dysfunction and BPH were based on the high cost of the named product and need to be revised now that cheap generic products are widely available.

Declaration of interests

Geoff Hackett has no interests to declare. Mike Kirby has received funding for advice, research and educational events from the pharmaceutical industry.

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