



# Should All Men with Type 2 Diabetes Be Routinely Prescribed a Phosphodiesterase Type 5 Inhibitor?

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Important health problems in men such as type 2 diabetes (T2DM), insulin resistance, erectile dysfunction, benign prostatic hyperplasia and depression have been shown to have to share common pathological processes, such as endothelial dysfunction and inflammation. This paper discusses the role of phosphodiesterase type 5 (PDE5) inhibitors, through beneficial effects on endothelial function and mediators of chronic inflammation and the possibility to treat or preventing these common conditions. We explore possible barriers to this approach, namely the lack of multiple product licences to treat each of these conditions and how these can be overcome by involving the patient in personalised decisions. We also discuss how opportunities are lost by patients with multiple medical conditions being referred to specialists, primarily interested in one specific problem, with little motivation to treat or prevent conditions outside their remit. We explore how these problems might be related to time and financial restraints or simply a lack of awareness of evidence published in journals related to other specialities. As specialists, we often pride ourselves on providing “personalised” or “patient centred” care, but we can only truly be doing so if we assess the specific needs of the patient across a range of conditions. As part of personalised care in T2DM, we routinely prescribe statins, angiotensin converting enzyme inhibitors and metformin, often with poor compliance. In this paper we explore whether the licensed daily PDE5 inhibitor tadalafil should be added routinely to this list as it will potentially improve and prevent bothersome symptoms and improve compliance with other medications.

**Keywords:** Cardiovascular diseases; Diabetes mellitus, type 2; Erectile dysfunction; Lower urinary tract symptoms; Phosphodiesterase type 5 inhibitors; Prostatic hyperplasia

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## INTRODUCTION

Type 2 diabetes (T2DM) is a major health and economic concern for the Western World. In the UK in 2018, 26% of the population over 65 are diagnosed, and 56% of these are men. The prevalence is 6 times greater in men of South East Asian origin and 3 times

greater in men of Afro-Caribbean background [1]. In the US, two-thirds of men over 65 have T2DM. The United Kingdom Prospective Diabetes Study (UKPDS) confirmed that each increase of 1% increases risk of diabetes related death by 21%, myocardial infarction (MI) by 14%, and peripheral vascular disease by 43% [2]. Currently all men diagnosed with T2DM over age

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40 are routinely commenced on metformin, statin and angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), as preventive strategies according to the National Institute for Health and Care Excellence (NICE) guidance [3]. In an age of “personalised” care in diabetes, we analyse the journey of a well-informed, newly diagnosed patient with T2DM to evaluate the current evidence for routine use of phosphodiesterase type 5 (PDE5) inhibitors.

## A PATIENT EXPERIENCE

This is an imaginary case based on the author’s experience. The names of the characters are fictitious.

Roger is an experienced solicitor, 50, has been recently diagnosed with T2DM at a routine medical with hemoglobin A1C 6.6 mmol/mol (International Federation of Clinical Chemistry and Laboratory Medicine,

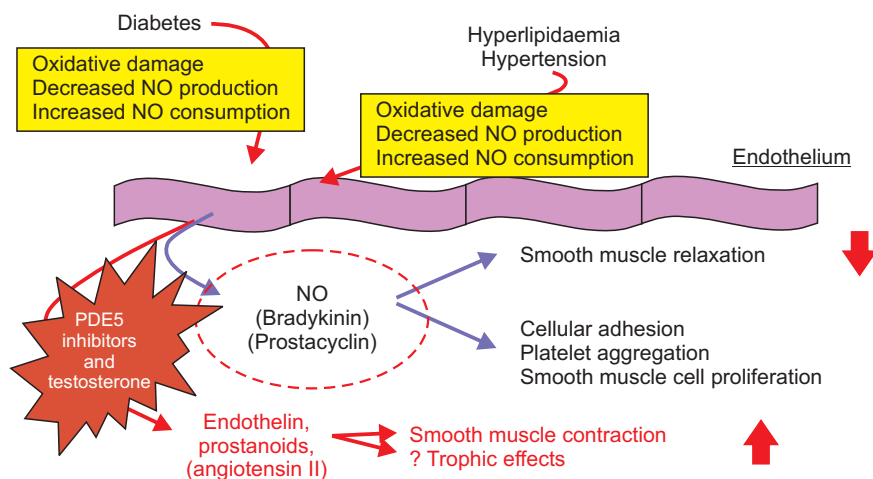
48%). He is slightly overweight (body mass index, 28.5 kg/m<sup>2</sup>), blood pressure 125/80 mmHg, total cholesterol 5.1 mg/dL, and high-density lipoprotein 1.6 mg/dL. He is otherwise fit, exercises regularly and is happily married to Janet for 20 years. His father was diagnosed with T2DM in his 50s, suffered from leg ulcers and died of a heart attack at 64. Roger’s sex life is OK but not what it used to be, and he passes urine a lot more frequently, especially at night and with a weak stream. He explains that his father also had an enlarged prostate, kidney failure and required two transurethral resections of the prostate. His general practitioner (GP) commences him on ramipril 5 mg, atorvastatin 20 mg and metformin 500 mg twice daily, explaining that this is routine for all patients. He is not asked about my erections, despite the NICE guidance, so he asks the diabetes nurse what the diagnosis of T2DM means for his sex life. She seems very surprised to be asked and offers reassurance plus a leaflet for newly diagnosed patients that mentions nothing about erectile dysfunction (ED).

**Table 1.** Erectile dysfunction in type 2 diabetes mellitus (related to duration, control and number of complications)

- Autonomic neuropathy
- Peripheral neuropathy
- Hypertension
- Peripheral vascular disease
- Dyslipidemia
- Drug side effects
- Benign prostatic hyperplasia (lower urinary tract symptoms)
- Depression
- Hypogonadism (double risk)
- Psychological Factors
- Plus ejaculatory disorders. Retrograde/Anejaculation
- Reduced sensation

## ERECTILE DYSFUNCTION

Roger does some research and is shocked to read that he has a 70% chance of developing ED [4] with a 55% (at best) response to oral therapy once the problem is diagnosed [5]. He wonders why he is taking 3 medications to prevent complications with a much lower incidence. He reads that ED in diabetes is due to multiples mechanisms (Table 1) primarily “endothelial dysfunction”, which is a chronic disorder potentially affecting all his blood vessels, with ED presenting first as it is



**Fig. 1.** Mechanism of endothelial dysfunction in type 2 diabetes. NO: nitric oxide, PDE5: phosphodiesterase type 5.

affecting smaller arteries [6] (Fig. 1). He reads that ED with diabetes increases his risk of heart disease within 3–5 years by 50% [7]. Further research suggests that an ARB might have been better for his erections than an ACE inhibitor, and he wonders why this was not discussed [8].

He reads that, as a newly diagnosed man with T2DM, he has a 30% chance of diabetic peripheral neuropathy (DPN) [2], and 32% increased risk of lower urinary tract symptoms/benign prostatic hyperplasia (LUTS/BPH [9]).

Roger returns to see his GP as he is having problems sustaining an erection and is prescribed 4 tablets of sildenafil 25 mg. Roger asks whether his testosterone might be measured as he has seen on the internet that men with T2DM may have a low testosterone but his GP points to Roger's fine beard and concludes that he is unlikely to have such a problem.

Roger and Janet have been used to a very active sex life, but they restrict activity to once per week after receiving the prescription, but they find the planning awkward and the medication ineffective. Roger is also noticing that his stream is getting worse and he is getting up to pass urine 3 times per night. His GP increases his sildenafil to 50 mg and gives him 4 further tablets. He performs a digital rectal examination and checks his prostate-specific antigen and commences tamsulosin 400 µg daily having confirmed a "slightly enlarged" prostate. Roger discontinues both medications after 2 weeks as he is losing his erection and finds it impossible to ejaculate. He is feeling depressed about the whole situation.

## **CURRENT NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE, AMERICAN DIABETES ASSOCIATION, AND EUROPEAN UROLOGICAL ASSOCIATION GUIDANCE**

Essentially the care that Roger has received is in line with current UK practice for BPH [10]. Although the NICE Guidance in T2DM [3] suggests annual assessment of ED, reviews by Schartau et al [11] and David et al [12] shows that this happens in less than 25% of men. In fact, Schartau et al [11] showed that, only for 1 year in 2013 did this improve, when GPs were specifically paid in their contact. When this payment was

withdrawn in 2014, the impact was lost. This effect was mirrored in a transient increase in prescribing of ED drugs and testosterone measurement. These findings suggested that financial payment was a major driver for changes in practice [11]. NICE advice is that men with T2DM and ED should be offered "a PDE5 inhibitor with the lowest acquisition cost", which is sildenafil 25 mg and "4 tablets per month maximum" [3]. Multiple randomized controlled trials (RCTs) have shown that, at best 50% of patients succeed with "on-demand" PDE5 inhibitors even at the highest dose and with unrestricted medication [13]. The mechanism of ED in T2DM is predominantly endothelial dysfunction, a chronic pathology affecting the entire cardiovascular symptom, such that a single tablet of sildenafil with a half-life of 4 hours is unlikely to affect the underlying progressive pathological process. The multiple pathologies involved in ED in T2DM are outlined in Table 1. Effectively Roger was unlikely to achieve success [13].

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 [9] but first line NICE advice for men with minimal prostate enlargement is an alpha-blocker [10], known to adversely affect ejaculation, which may already be affected by neuropathy in men with T2DM [9]. In addition, the co-prescribing with an on-demand PDE5 inhibitor is more likely to produce symptomatic hypotensive episodes in men with T2DM [14,15], due to co-morbid autonomic neuropathy, co-prescribed anti-hypertensives and hypoglycaemia.

European Urological Association and British Society for Sexual Medicine (BSSM) guidelines [16,17] do recommend daily tadalafil as first line for men with ED and LUTS but unfortunately this strategy is not even considered by NICE, nor are Diabetes specialists likely to be motivated to follow urology or sexual medicine guidelines.

Likewise, American Urological Association [18], American Diabetes Association [19], American Association of Clinical Endocrinologists [20] and BSSM guidelines [21] do 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 ED, even after 21 years of PDE5 inhibitors.

## THE CASE FOR DAILY TADALAFIL 5 mg FOR ENDOTHELIAL DYSFUNCTION IN MEN WITH TYPE 2 DIABETES

ED is now acknowledged as an independent risk factor for cardiovascular events and mortality [17,22], increasing the risk by 50% in men with T2DM. ED has now been introduced into cardiovascular risk calculators [23]. Modern cardiovascular risk strategies revolve around reducing the impact of the modifiable risk factors as demonstrated in the INTERHEART study [24]. It is therefore logical that ED 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 chronic PDE5 inhibitors in many studies [3]. Rosano et al [25] demonstrated significant improvement in endothelial function after 2 weeks, that persisted 2 weeks after treatment cessation. Amano et al [26] investigated 81 men with ED and LUTS treated with tadalafil for 12 months and found significant improvements in international index of erectile function (IIEF) at 3 months (continuing improvement at 12 months), international prostate symptom score (IPSS) after 1 month, brachial-ankle pulse wave velocity and ankle-brachial index after 3 months. Ramirez et al [27] investigated 21 men with pre-diabetes treated with sildenafil 50 mg daily for 3 months and found significant improvements in insulin sensitivity, PA-1 and albumen-creatinine ratio. Santi et al [28] investigated 54 men with T2DM in a 24-week placebo-controlled study of vardenafil 10 mg BD and found significant improvements in IIEF, Flow mediated dilatation, interleukin (IL)-6, and testosterone levels in the cohort with hypogonadism. Aversa et al [29] investigated 45 men with diabetes treated with either 5 mg tadalafil daily or 20 mg on-demand and found that only daily tadalafil improved flow mediated dilatation, insulin sensitivity and lean muscle mass. Fiore et al [30] demonstrated positive changes in adipocytes and browning of fat in obese men undergoing biopsy of visceral fat after only 7 days 100 mg of sildenafil *vs.* placebo.

Santi et al [31] conducted a meta-analysis of 12 RCTs (n=476) of chronic PDE5 inhibitors 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 (25–100 mg daily), usually for 12-week maximum duration.

Lee et al [32] conducted a 12-week study of tadalafil 5 mg daily in men with T2DM and found that severity of ED was related to baseline hs-CRP. Response rate, based on Sexual Encounter Profile (SEP) 3 was 70%. Median hs-CRP levels were 0.31 mg/dL (range, 0.18–0.62 mg/dL) in non-responders and 0.14 mg/dL (range, 0.09–0.4 mg/dL) in responders, respectively (p=0.028).

Schwartz et al [33] reviewed studies of tadalafil 5 mg daily on endothelial function and suggested that these effects might translate into a long-term reduction in cardiovascular risk.

## DAILY TADALAFIL EFFECTS ON TESTOSTERONE LEVELS

Men with T2DM have low levels of testosterone in up to 40% with associated cardiovascular risk [1]. Many may be candidates for testosterone therapy to improve sexual symptoms, quality of life and cardiovascular risk. Hellstrom et al [34], in a placebo-controlled study designed to assess sperm parameters in 253 men treated with tadalafil 20 mg for 3 months found significant increases in total testosterone *vs.* placebo and no significant effect on semen parameters over 3 cycles. Ozcan et al [35] treated 40 men with metabolic syndrome with tadalafil 5 mg for 3 months with an increase of testosterone from 11.4 (baseline) to 16.5 nmol/L, and IIEF-5 from 11.3 to 19. The authors recommend tadalafil 5 mg once daily in those men with ED especially low testosterone levels accompanied by metabolic syndrome. Spitzer et al [36] treated 106 men with sildenafil 50–100 mg for 3–7 weeks (mean 2.6 doses on demand per week) and found a mean rise of 3.6 nmol/L and corresponding fall in luteinizing hormone. 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. 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.

## THE CASE FOR TADALAFIL 5 mg DAILY FOR ERECTILE DYSFUNCTION IN MEN WITH TYPE 2 DIABETES

Unfortunately, PDE5 inhibitors do not have a licence to treat the process of endothelial dysfunction and are only licensed to treat ED and pulmonary hypertension (sildenafil and tadalafil) [33]. Tadalafil 5 mg daily is licensed to treat LUTS/BPH and is the only PDE5 inhibitor licensed for daily use [14,16]. Physicians employed under health care systems are advised to prescribe only for licensed indications. However, patients should be informed if the choice of one licensed formulation over another confers other health benefits even if that therapy may require funding by the patient. The important question is therefore “does daily tadalafil in T2DM produce better results in terms of sexual function compared with other therapies”? Many “preference studies” were set up to address this question, with conflicting findings largely due to selection bias, inappropriate patient reported outcomes and different dosing advice for different preparations. In the most recent meta-analysis of 16 head to head trials of sildenafil and tadalafil, Gong et al [13] concluded “Tadalafil shares a similar efficacy and safety with sildenafil but tadalafil significantly improves patients’ sexual confidence and quality of life according to multiple outcome measures. Furthermore, patients and their partners prefer tadalafil to sildenafil. Hence, tadalafil may be a better choice for ED treatment” [13]. Park et al [37] assigned

118 men with T2DM and ED to either tadalafil 20 mg on demand or tadalafil 5 mg daily and followed them up for 2 years. The IIEF score improved progressively with daily 5 mg, but not on demand tadalafil 20 mg, 7.2 vs. 2.4 ( $p < 0.0001$ ).

The BSSM guidelines 2018, report that on-demand PDE5 inhibitors are only successful in 50% of men with T2DM [17] despite unlimited medication in clinical trials. Buvat et al [38] reported that 89% of patients switched to daily tadalafil were still taking medication after 12 months. The BSSM guidelines suggest that up to 50% of patients who fail with on-demand therapy respond to daily dosing [17].

Five meta-analyses have compared on-demand vs. daily tadalafil and the findings are reported in Table 2. Brock et al [39] compared only RCTs and concluded equal efficacy but these trials were usually of 12-week duration where on-demand patients were provided with unlimited medication such that total dose of tadalafil was usually significantly higher than 5 mg daily dosing. Bansal et al [40] reviewed 6 head to head studies of up to 12 weeks and concluded that daily tadalafil resulted in a 1.82 higher ED score than 20 mg on-demand. Peng et al [41] included studies of up to 26 weeks and found superiority for tadalafil 5 mg daily especially in men with diabetes and post radical prostatectomy and especially when assessed by SEP, a diary completed daily as opposed to IIEF data which relies on memory of sexual attempts up to 6 months previously. Prasetyo [42] also concluded greater efficacy for once daily (OaD)

**Table 2.** Meta-analyses of daily (OAD) tadalafil vs. on-demand tadalafil

Study	Head to head RCTs reviewed	Conclusions
Brock et al (2016) [39]	17 prn vs. placebo, 4 OAD vs. placebo (n=4,345) Usually 14 weeks duration	Efficacy for both treatments across a wide range of pathologies – no significant difference between regimes.
Bansal et al (2018) [40]	6 RCTs, 2 open label (n=672) 12 weeks duration	Efficacy across a wide range. Erectile function score 1.82 greater for OAD. SEP2 and 3 not assessed.
Peng et al (2017) [41]	6 RCTS OAD vs. on vs. demand (n=1,534) 8 weeks to 9 months duration	Efficacy for both treatments across wide range of pathologies. Superiority for OAD in terms of SEP2 and SEP3, especially in prostate cancer. Patient preference for OAD.
Prasetyo et al (2019) [42]	4 RCTS (n=1,200) Under 14 weeks duration	Both treatments efficacious but SEP2 and SEP3 superior for OAD tadalafil.
Zhou et al (2019) [43]	4 RCTS (n=1,035) Greater than 24 weeks SEP2 and 3 was main outcome.	SEP2 MD 10.08 ( $p < 0.00001$ ) and SEP3 MD 8.09 ( $p < 0.009$ ). Tadalafil provided greater efficacy and lower side effect profile in RCTs >24 weeks.

OAD: once daily, RCTs: randomized controlled trials, prn: pro re nata (when needed), SEP2: Sexual Encounter Profile Question 2 (Were you able to achieve an erection suitable for penetration?), SEP3: Sexual Encounter Profile Question 3 (Were you able an erection suitable for the completion of sexual activity?), MD: mean difference.

*vs.* on-demand tadalafil based on SEP2 and SEP 3 data. Most recently Zhou et al [43] conducted a meta-analysis of 4 studies longer than 26 weeks and concluded that daily tadalafil was associated with greater therapeutic benefit and lower side effect profile and that efficacy increased with duration of therapy. This is an important finding, bearing in mind the progressive deterioration in endothelial function and autonomic neuropathy associated with diabetes and suggests that therapy needs to address the pathological damage and not purely a symptom. Shafik et al [44] demonstrated that loss of morning erections was associated with atrophy of the tunica albuginea and veno-occlusive dysfunction and chronic dosing with PDE5 inhibitors is more likely to prevent this progressive decline.

The impact of tadalafil daily dosing on women partners' satisfaction with sexual activity has also been a topic of recent interest and research. A partner preference study of on-demand sildenafil *vs.* tadalafil indicated that 79% of women partners preferred tadalafil, citing a more relaxed approach to sexual intimacy and greater flexibility with respect to timing of intercourse [45]. Based on this, it may be inferred that the flexibility of completely separating medication from sexual activity (as is the case for daily dose therapy) would be appealing to many women partners of men with ED. Women who dislike the idea of partners taking ED therapy might readily accept that their partner takes therapy for "bothersome" BPH and that erections improve as part of that regime.

## THE CASE FOR EARLY INTERVENTION OR PREVENTION OF ERECTILE DYSFUNCTION

Several studies suggest that the prevalence of ED in T2DM as assessed by IIEF-5 score of 21 or less is 75% to 77% and is related to duration of diabetes, number of complications and quality of glycaemic control [17]. If current approaches to therapy result in 50% of patients failing to respond to oral therapy, then large numbers are progressing to second- and third-line therapies that, in an age of generic oral drugs results in exponentially higher costs. There are now sound economic reasons for earlier intervention with therapy targeted towards the chronic disease progress, or even prevention. It could be argued that ED progression is virtually inevitable as very few men with T2DM have completely normal

IIEF scores and ED often pre-dates the diagnosis of T2DM [46].

As ED is a recognised risk factor that confers an increased cardiovascular risk of 50%, then logically ED to be prevented as would be the case with any other risk factor [22,47]. Regular erections and sexual activity have been shown to protect against ED [48]. It might be reasonable to present these facts to the patient and his partner and allow them to be involved in the discussion as to which stage he would wish daily therapy or even early prevention. Clearly lifestyle advice in relation to ED should always be given at the same time but such interventions should have been implemented as part of standard diabetes care [9,17].

## ECONOMIC ISSUES

Generic tadalafil 5 mg costs approximately £5 per month at National Health Service tariff. Every patient in the 45% who subsequently fail with the PDE5I will cost £12–15 for each dose of second line therapy, such as alprostadil or MUSE<sup>®</sup>, meaning £48–60 per month for sexual activity once per week or £96–120 per month for activity twice per week [49]. Each case will usually require secondary care referral at £120 with an average of three follow-up visits at £80 to teach the injection process. Costs will be greater under health care systems where the patient pay privately. Involving the patient in discussions about the finances of long-term treatment might result in a positive decision towards early therapy or even prevention.

## THE CASE FOR TADALAFIL FOR SYMPTOMATIC LOWER URINARY TRACT SYMPTOMS/BENIGN PROSTATIC HYPERPLASIA IN MEN WITH TYPE 2 DIABETES

Over 50% of men over 50 have symptomatic BPH/LUTS and men with T2DM have a 32% increased risk [4,50]. Among the mechanisms involved in the pathology of BPH/LUTS, the nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) pathway has an important functional role, and all key enzymes of this pathway, NO synthase, protein kinase G-1 and PDE5 are expressed in the prostatic tissue. NO exerts a general inhibitory effect of muscle tone on the lower urinary tract. A decrease in NO-mediated relaxation

of smooth prostatic muscle contributes to BPH/LUTS pathology. Latest evidences on the pathophysiology of BPH/LUTS has provided the rationale for use of PDE5-inhibitors: improvement of lower urinary tract (LUT) oxygenation, smooth muscle relaxation, negative regulation of proliferation and trans-differentiation of LUT stroma, reduction of bladder afferent nerve activity, and down-regulation of prostate inflammation are the proven mechanisms of action of PDE5-inhibitors [51].

Head to head trials show equal efficacy for tadalafil compared with tamsulosin, with clinically significant reduction of 5–6 IPSS points but greater patient preference for tadalafil, irrespective of improvements in ED [52,53]. Initial studies failed to show an increase in flow rate but a review by Roehrborn et al [54] in total study population of 1,500 men, patients with tadalafil had significantly greater maximum urinary flow rate (Q<sub>max</sub>) improvement (mean, +1.1 mL/s) compared with patients with placebo (mean, +0.4 mL/s; *p*=0.003), significant Q<sub>max</sub> improvement in the total study population was mainly driven by effects in patients who voided 250–450 mL (*p*=0.011) and had a baseline Q<sub>max</sub> 10–15 mL/s (*p*=0.044). Pogula et al [55] published a 12-week comparative study of tadalafil *vs.* tamsulosin in BPH and found superiority for tamsulosin in terms of IPSS and Q<sub>max</sub> but marked superiority for tadalafil for IIEF. A review by Hatzimouratidis [56] pointed out that head to head comparison in 12-week studies were unhelpful due to the different mechanism of action of the drugs, improvement of co-morbid ED and that long-term studies of disease progression are more relevant. Donatucci et al [57] showed that IPSS scores with tadalafil were still improving after 1 year of open label use and that improvements in erectile function were maintained.

One RCT showed significant improvement with tadalafil 5 mg daily in the bothersome symptom of post-micturition dribble, whereas tamsulosin has proved ineffective [58]. Studies suggest a synergistic effect with tadalafil in combination with tamsulosin, and, for larger prostates with finasteride. A recent UK DATA-LINK study has suggested a possible 30% increased risk of T2DM in men taking 5 $\alpha$ -reductase inhibitors, and caution in their use in men with metabolic syndrome [59].

A recent meta-analysis supported the rationale for tadalafil/finasteride in terms of preservation in sexual

function in comparison with tamsulosin/finasteride, an effect likely to be more important in men with BPH and T2DM where multiple co-morbidities for ED are likely to be present [60].

## THE CASE FOR TADALAFIL FOR BENIGN PROSTATIC HYPERPLASIA PREVENTION IN TYPE 2 DIABETES

Over two-thirds of men over 50 with T2DM suffer from some degree of LUTS as assessed by IPSS [4]. Alpha-blockers, as first line BPH therapy for decades, are more likely to be associated with drug interactions and hypotension in men with T2DM, especially those on multiple anti-hypertensive regimes or those subject to hypoglycaemia. Older, frail men treated with alpha-blockers may be at greater risk of falls, especially related to increased micturition at night [61].

Alpha-blockers have consistently shown to have no effect of BPH progression as sole therapy [62]. BPH progression has considerable health economic consequence that add to the huge economic burden of T2DM [62]. Long-term data on prostate size and disease progression with tadalafil are required to address this question but a review by Gacci et al [63] suggests that improved endothelial dysfunction and reduction of inflammatory markers suggest optimism that daily tadalafil might reduce BPH progression. As 75% of men with T2DM are likely to suffer ED and ejaculatory problems due to vascular and neuropathic complications of T2DM, studies reporting “volunteered” sexual complications are highly likely to underestimate the true impact of both alpha-blockers and finasteride, as reported by Seftel et al [64]. The MSAM-7 study clearly showed the close association of LUTS severity with lower IIEF scores [50].

## EVIDENCE THAT PHOSPHODIESTERASE TYPE 5 INHIBITORS MIGHT REDUCE DIABETES RELATED MORBIDITY AND MORTALITY

PDE5 inhibitors were developed as daily therapy to treat cardiovascular disease and improvements in ED were an incidental finding during clinical trials [3]. Sildenafil and tadalafil are licensed to treat pulmonary hypertension through their beneficial effects on

endothelial dysfunction [3]. Several cardiology reviews have highlighted the beneficial cardiovascular effects that would potentially reduce cardiovascular events in high risk populations such as men with T2DM [3,65-67]. Beneficial mechanisms include improved endothelial function, enhanced cGMP and cyclic adenosine monophosphate (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 [65]. These mechanisms are highlighted in Fig. 2. Currently tadalafil 5 mg is the only PDE5 inhibitor suitably licensed for daily use [17].

Anderson et al [68] who followed a UK primary care population of 5,956 UK men with T2DM over 6.9 years. A 31% reduction in all-cause mortality and 26% reduction in MI were reported in men taking PDE5 inhibitors. Only 22.8% of men with T2DM had been prescribed a PDE5 inhibitors, with patients usually restricted to once per week. These findings were supported by Hackett et al [69] in a prospective RCT of testosterone therapy in T2DM. The 175 men taking PDE5 inhibitors showed a significant and independent reduction in all-cause mortality.

Andersson et al [70] reported data from a Swedish database of 43,415 men after first MI for 5 years and found significant reduction in all-cause and cardiovascular mortality and 30% reduction in new diagnosis in heart failure and related admissions, in men prescribed PDE5 inhibitors. The benefits were greater in men on more frequent dosing of PDE5 inhibitors and were not

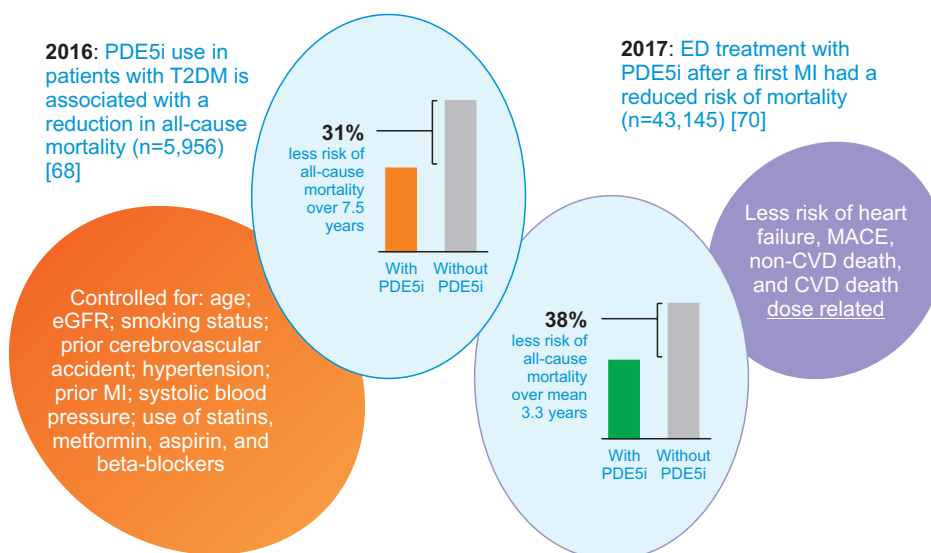
seen with other ED therapies.

These 3 studies are subject to potential bias. Men prescribed PDE5 inhibitors would have been likely to have been assessed as “fit or sexual activity” and men taking nitrates would have been excluded. Conversely men prescribed a PDE5 inhibitor would have been suffering from ED, which is known to be associated with 50% additional risk of a cardiovascular event. These studies suggest the need for a long-term placebo-controlled study to address the potential cardio-protective role of daily PDE5 inhibitors in T2DM but such a study might be problematic given the high rates of ED and the logistic of a placebo arm of several year duration for a highly symptomatic condition such as ED.

Scranton et al [71] carried out a complex health care review and concluded that diagnosis and successful treatment of concomitant ED may promote improved adherence and management of comorbid diseases. Concomitant ED management may improve treatment outcome, decrease healthcare costs, and possibly prevent or even improve deterioration in medical conditions comorbid with ED.

## PREVENTION OF DIABETIC PERIPHERAL NEUROPATHY

DPN 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 PDE5 inhibitors. NO is the major



**Fig. 2.** Phosphodiesterase type 5 inhibitors (PDE5is) for cardio-prevention observational studies. T2DM: type 2 diabetes, ED: erectile dysfunction, MI: myocardial infarction, eGFR: epithelial growth factor receptor, MACE: major adverse cardiac events, CVD: cardiovascular diseases.



neurotransmitter of the vasa nervorum, suggesting an important preventive role in microvascular complications. Currently, drugs used to treat established DPN effectively block pain pathways and frequently aggravate ED. There is huge potential for savings by the prevention of complications of DPN [72,73].

## DIABETIC NEPHROPATHY

The multiple potential benefits of PDE5 inhibitors in renal disease are as follows; decreases in ischemia reperfusion injury, improves endothelial dysfunction, decreases apoptosis and necrosis, increases NO availability and endothelial nitric oxide synthase, increases mitochondrial biogenesis, decreases DNA damage, decreases renal inflammation, decreases renal fibrosis, increases catalase, increases superoxide dismutase, inhibits lipid peroxidation, decreases activation of and proliferation of mesangial cells, preserves podocyte function and suppresses vascular smooth muscle cell proliferation in the glomerular arterioles [74].

## CANCER PREVENTION

T2DM is associated with increased risk of many cancers, particularly colon. Review articles suggested a role for PDE5 inhibitors in cancer prevention [75]. In a Swedish national database study, Huang et al [76] studied a total of 4,823 patients who were prescribed PDE5 inhibitors during the study period; the incidence rate of colorectal cancer (CRC) was 2.64 per 1,000 person-years for men prescribed PDE5 inhibitors compared with 4.46 per 1,000 person-years for men without a prescription. They found a significant negative association between PDE5 inhibitor use and risk of CRC (adjusted hazard ratio, 0.65; 95% confidence interval, 0.49–0.85); the decreased risk of CRC was associated with an increased cumulative dose of PDE5 inhibitors ( $p=0.003$ ).

## COGNITIVE IMPROVEMENT

Choi et al [77] treated 30 men with ED and mild cognitive impairment with tadalafil 5 mg for 8 weeks. Mean baseline IIEF and Montreal Cognitive Assessment (MoCA) scores were  $7.52\pm 4.84$  and  $18.92\pm 1.78$ . After the eight-week treatment, mean IIEF and MoCA scores were increased to  $12.92\pm 7.27$  ( $p<0.05$ ) and  $21.8\pm 1.71$  ( $p<0.05$ ), respectively. Patients showed

increased relative regional cerebral blood flow in the postcentral gyrus, precuneus, and brainstem after tadalafil administration *versus* at baseline ( $p<0.001$ ).

Urios et al [78] studied 9 patients with LUTS/BPH and ED. Patients with BPH/LUTS-ED showed increased CD4+CD28<sup>+</sup> autoreactive T-cells ( $p<0.05$ ), and higher levels of pro-inflammatory ILs (IL-6,  $p<0.001$ ; IL-17 and IL-18,  $p<0.05$ ), compared to controls. Patients achieved lower scores than controls in psychometric tests assessing mental processing speed and attention ( $p<0.05$ ), and showed lower amplitude ( $p<0.01$ ) and area ( $p<0.05$ ) of mismatch negativity (MMN) wave than controls. Inflammatory, psychometric and electrophysiological parameters were normalized after tadalafil treatment. The authors concluded that there is a pro-inflammatory environment in blood in patients with BPH/LUTS-ED which would induce cognitive impairment and alter MMN. Phosphodiesterase-5 inhibition with tadalafil exerts anti-inflammatory effects and ameliorates cognitive function and MMN parameters. The authors concluded that tadalafil could be a promising candidate for chronic treatment in other inflammatory pathologies associated with mild cognitive impairment.

## DEPRESSION

Depression is twice as common in men with T2DM with prevalence of 25% [79] and sexual dysfunction is the complication of T2DM most closely linked with depression. Both ED and LUTS are linked with depression [80]. Nurnberg et al [81] showed that depression score improved when men with ED and moderate depression were treated with sildenafil *versus* placebo. Shim et al [82] conducted a 2 month placebo controlled in 60 men with ED and with no known cognitive impairment. The changes in the Patient Health Questionnaire (PHQ)-9 and PHQ-15 were  $2.04\pm 3.14$  and  $2.17\pm 2.87$  with the PDE5 inhibitor, udenafil given daily, and  $1.20\pm 1.63$  and  $0.56\pm 2.48$  in the placebo group (both,  $p<0.001$  for udenafil). The authors concluded that daily dosing with a PDE5 inhibitor seems to improve cognitive function, depression and somatization, as well as erectile function, in patients with ED.

## CONCLUSIONS – BACK TO THE PATIENT

Roger returns to his GP with a balanced argument based on his comprehensive research. He states that the impact of ED and BPH are far more relevant for him now than statistical risk reduction for cardiovascular outcomes. He feels that it is more relevant to take a daily medication likely to produce symptomatic improvement within days. From what he has read, the major strategy for improving outcome in T2DM is multiple rather than selective risk factor reduction. He witnessed the poor quality of life that his father experienced with BPH, whilst still a relatively young man and would rather take a treatment that addresses the pathological processes of BPH rather than one repeatedly shown to have no impact on the progression of the disease. He has already experienced mild muscular aches possibly related to his statin, nausea and loose stools with metformin and an irritant cough with ramipril, which eased when he was eventually switched to valsartan. He experienced no side effects with on-demand sildenafil, so is confident that tadalafil at 5 mg will have no adverse effects apart from more frequent erections, which would be greatly appreciated. Unfortunately, his GP states that currently he is restricted from prescribing daily tadalafil and must, under NICE guidance, only prescribe the PDE5 inhibitor with lowest acquisition cost. Roger leaves having decided that he will stop the array of vitamins and antioxidants, taken for many years at vast expense, having read that they do little good and possible harm. He decides to use the savings to self-fund low cost generic tadalafil 5 mg daily. As he leaves, he picks up a diabetes UK leaflet, stressing the importance of targeted, individualised care in diabetes and wonders whether this is what he has been receiving.

Prescribing policies for T2DM are largely decided by diabetes specialists, with priorities given to glycaemic control. Co-morbid conditions such as ED and BPH are usually managed by urologists and publications concerning PDE5 inhibitors largely in urology and sexual medicine journals. The recognition of ED as an independent risk factor for coronary heart disease justifies inclusion in routine risk reduction strategies. Evidence that PDE5 inhibitors produce benefits through multiple mechanisms now supports routine prescribing in diabetes care, not least because the patients will poten-

tially experience symptomatic improvements that will increase compliance with other prescribed interventions.

### Conflict of Interest

The author has nothing to disclose.

### Author Contribution

Conceptualization: GH. Data curation: GH. Formal analysis: GH. Investigation: GH. Methodology: GH. Project administration: GH. Resources: GH. Software: GH. Supervision: GH. Validation: GH. Visualization: GH. Writing – original draft: GH. Writing – review & editing: GH.

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