The treatment rate of erectile dysfunction (ED) in younger men with type 2 diabetes is up to four times higher than the equivalent non-diabetes population

Mike Stedman1 | Martin B. Whyte2 | Mark Lunt3 | Marco Albanese4 | Mark Livingston5 | Roger Gadsby6 | Geoff Hackett7 | Simon G. Anderson8,9 | Adrian H. Heald3,10

1Res Consortium, Andover, Hampshire, UK
2Clinical and Experimental Medicine, University of Surrey, Guildford, UK
3The School of Medicine and Manchester Academic Health Sciences Centre, University of Manchester, Manchester, UK
4Herzzentrum Hirslanden Zentralschweiz, Luzern, Switzerland
5Black Country Pathology Services, Walsall Manor Hospital, Walsall, UK
6Warwick Medical School, University of Warwick, Coventry, UK
7Aston University, Birmingham, UK
8The George Alleyne Chronic Disease Research Centre, Caribbean Institute of Health Research, University of the West Indies, Bridgetown, Barbados
9Division of Cardiovascular Sciences, University of Manchester, Manchester, UK
10Salford Royal Hospital, Salford, UK

Correspondence
Adrian Heald, Department of Diabetes and Endocrinology, Salford Royal Hospital, Salford M6 8HD, UK.
Email: adrian.heald@manchester.ac.uk

Abstract

Introduction: Erectile dysfunction (ED) is common in older age and in diabetes mellitus (DM). Phosphodiesterase type 5-inhibitors (PDE5-is) are the first-line for ED. We investigated how the type of diabetes and age of males affect the PDE5-i use in the primary care setting.

Methods: From 2018 to 2019, the general practice level quantity of all PDE5-i agents was taken from the general practice (GP) Prescribing Dataset in England. The variation in outcomes across practices was examined across one year, and for the same practice against the previous year.

Results: We included 5761 larger practices supporting 25.8 million men of whom 4.2 million ≥65 years old. Of these, 1.4 million had T2DM, with 0.8 million of these >65. About 137 000 people had T1DM. About 28.8 million tablets of PDE5-i were prescribed within the 12 months (2018-2019) period in 3.7 million prescriptions (7.7 tablets/prescription), at total costs of £15.8 million (£0.55/tablet). The NHS ED limit of one tablet/user/wk suggests that 540 000 males are being prescribed a PDE5-i at a cost of £29/y each. With approximately 30 000 GPs practising, this is equivalent to one GP providing 2.5 prescriptions/wk to overall 18 males. There was a 3x variation between the highest decile of practices (2.6 tablets/male/y) and lowest decile (0.96 tablets/male/y). The statistical model captured 14% of this variation and showed that T1DM males were the largest users, while men age <65 with T2DM were being prescribed four times as much as non-DM. Those T2DM >65 were prescribed 80% of the non-DM amount.

Conclusion: There is a wide variation in the use of PDE5-is. With only 14% variance capture, other factors including wide variation in patient awareness, prescribing rules of local health providers, and recognition of the importance of male sexual health by GP prescribers might have a significant impact.
1 | INTRODUCTION

Erectile dysfunction (ED) is a consequence of both older age and diabetes (DM). Phosphodiesterase type 5-inhibitors (PDE5-is) are first-line therapy for the treatment of ED and, since their introduction in 1998, although licensed for use in men at increased cardiovascular risk, there remains reticence on the part of some doctors to prescribe them.

The United Kingdom National Health Service (UK NHS) funds prescribing of one tablet PDE5-i per week for ED in men: with diabetes, or on social support, or aged >60 years. In addition to PDE5-is, various therapies have been utilized for the treatment of sexual dysfunction in patients with diabetes mellitus including prostaglandins, testosterone, pentoxifylline, amongst others. Amongst the different medications, PDE5-is have been the mainstay of treatment due to the simplicity of dosing and wider patient acceptability. The various PDE5-is that have been evaluated in clinical trials in people with diabetes have included sildenafil, tadalafil, vardenafil, udenafil, mirodenafil, and avanafil.

We recently described that even ad hoc PDE5-i use is associated with reduced all-cause mortality in type 2 diabetes (T2DM). Furthermore, the use of a PDE5-i was also associated with lower mortality in those with a history of acute myocardial infarction (MI). These findings have been replicated in other populations of T2DM including the landmark UK Blast study in which PDE5-i use was associated with decreased mortality in a prospective intervention study.

We investigated whether the presence of diabetes modifies the relation of PDE5-i use with age and adjusted for variance between primary care centres. This national-level analysis is restricted to general practice (GP) prescribing data only which specifically does not capture over the counter and on-line purchases.

2 | METHODS

From 2018 to 2019, the Practice level data for the quantity of PDE5-is issued were taken from the GP Prescribing Dataset. All PDE5-is prescribed in England were included, specifically Sildenafil, Tadalafil, Avanafil, and Vardenafil. The population of males in each practice and their age categories was taken from the GP practice published data (2019). The number of people with T1DM and T2DM in each practice, as well as numbers of men with T2DM aged 65 years or more were taken from the National Diabetes Audit. The number of non-diabetes males was calculated from the difference between the previous two.

PDE5-i prescribing was analysed in males aged ≥30 years. The variation in outcomes across practices was examined across one year, and for the same practice against the previous year. The exposure variables were the proportion of males ≥65, the proportion of males in population with T2DM, the percentage of men with T2DM age ≥65, and the proportion of men with T1DM.

What's known
- Phosphodiesterase type 5-inhibitors are considered first-line therapy for the treatment of erectile dysfunction.
- They are licensed in individuals both with and without overt cardiovascular (CVD) risk factors, including type 2 diabetes (T2DM).

What's new
- There was a 3x variation between the highest decile of practices (2.6 tablets/male/y) and lowest decile (0.96 tablets/male/y).
- The statistical model captured 14% of this variation and showed that T1DM males were the largest users, while men age <65 with T2DM were being prescribed four times as much as non-diabetes mellitus (DM). Those T2DM >65 were prescribed 80% of the non-DM amount.
- With only 14% variance capture, other factors including wide variation in patient awareness, prescribing rules of local health providers, and recognition of the importance of male sexual health by general practice prescribers might have a significant impact.

There is a wide variation within GP practices across each of these factors, so multivariable regression modelling was used to assess the association between the exposure variables and expected PDE5-i prescribing outcome. The regression coefficients from this model were then applied to the adjusted exposure variable to extrapolate the expected outcomes in the following scenarios: Thus, there is one model with five variables with each variable extrapolated to 100%, while taking the others to 0%.

1. 100% men non-diabetes and age <65
2. 100% men non-diabetes and age ≥65
3. 100% men T2DM and age <65
4. 100% men T2DM and age ≥65
5. 100% men T1DM.

The NHS 1/tablet/wk (52/y) rule can be used to estimate the average actual number of patients being prescribed PDE5-i over the year.

3 | RESULTS

About 5,761 practices in 2018 (looking after 51.4 million patients or 90% of the population in England) were included. These practices supported 25.8 million men, of whom 16.4 million were ≥30 years
old, of these and 4.2 million ≥65 years old. Of these, 1.4 million had T2DM and 137 000 had T1DM.

A total of 28.8 million tablets of PDE5-i were prescribed within the 12 months (2018-2019) period in 3.7 million prescriptions (equivalent to 7.7 tablets/prescription) (Table 1), at total costs of £15.8 million (equivalent to £0.55/tablet). Based on the NHS ED limit of one tablet/male user/wk this suggests that 540 000 males are being prescribed this therapy at a cost to the NHS of around £29/y each. There are approximately 30 000 full-time equivalent GPs practising, so this is equivalent to each GP providing 2.5 prescriptions/wk to a total of around 18 males. Analysis of the volume of prescribing of PDE5-i in each practice was adjusted for the number of men over the age of 30 years on the practice list (Figure 1). This shows a 2.7-fold variation between the highest decile of practices (2.6 tablets/male/y) and lowest decile (0.96 tablets/male/y). There was little variation in PDE5-i prescribing year on year, with 85% of the variation between practices explained by the prescribing level in the previous year when comparing the periods 1 April 2017-31 March 2018 with the equivalent next 12 month period (Figure 2).

In the regression model, while all the chosen factors had $P$ values < .05, together they could explain only 14% of the variation between practices. Extrapolation using the regression coefficient taken from this model was used to identify population-level effects and showed that the majority of PDE5-is are being prescribed to older Non-DM males. ED treatment is most prevalent in T1DM men at a rate of approximately seven tablets per year (Table 1). There was much

### TABLE 1  PDE5-i prescribing in diabetes and non-diabetes men in England

| Class         | Model PDE5-i Use tablet/male/y | Actual Male Population Million | Model Total Tablets million | % of total PDE5i |
|---------------|--------------------------------|---------------------------------|----------------------------|------------------|
| Non DM 30-65 | 0.9                            | 10.65                           | 9.6                        | 34%              |
| Non DM ≥65   | 3.92                           | 3.26                            | 12.8                       | 45%              |
| T2DM <65     | 3.51                           | 0.66                            | 2.3                        | 8%               |
| T2DM ≥65     | 3.17                           | 0.79                            | 2.5                        | 9%               |
| T1DM         | 7.05                           | 0.13                            | 0.9                        | 3%               |
| Total        | 16.4                           | 28.1                            | DM = 20% of total          |

Abbreviation: DM, diabetes mellitus.

**FIGURE 1** Phosphodiesterase type 5-inhibitors (PDE5-i) across general practices in England
higher PDE5-i prescribing in younger T2DM men 3.51 tablets per year than in their non-DM counterparts at 0.9 tablets per year. There was a similar prescribing prevalence in older T2DM men and older non-DM males. A caveat in our analysis is that if local doctors are disregarding NHS rules and prescribing each user more than 52 tablets/y then the overall numbers of therapy users could be significantly lower.

4 | DISCUSSION

There is a wide variation in the use of PDE5-is, that persists year on year. Older age and T2DM are seen as some of the main sources of population ED. This model while including those two factors could only capture 14% of the variance in PDE5-i prescribing. This suggests that other factors require inclusion. This may include variation in patient awareness, rules for prescribing with local health providers, and recognition of the importance of male sexual health at the GP prescriber level.12

Men with diabetes should be routinely screened for ED as part of their annual review. However, men with ED are sometimes reluctant to report the condition to their doctor,12,13 compounded by physicians' barriers to managing ED in their practice.14,15 Conversely, lack of libido, as may be caused by testosterone deficiency which is very common in patients with diabetes, may influence patient demand for PDE5-is?

A significant component of the variance is factors that are not "visible" from the national level data that we considered. This would suggest that much of the differences between GP practices in PDE5-i prescribing relate to other population characteristics and individual factors at the level of the prescriber.

It may also be the case although PDE5-is are licensed to be used in people at elevated cardiovascular risk, they are not necessarily used due to unfounded fear of adverse effects.

Phosphodiesterase type 5-inhibitors may also improve cardiovascular health.7-9 We recently showed that PDE5-i use is associated with significantly reduced mortality in men with T2DM (therefore high-attendant cardiovascular risk). This effect remained after adjustment for known confounders.7 Hence the use of PDE5-is should not be considered hazardous men with T2DM.

The reported association between PDE5i use and reduced mortality, 70% of which is estimated to be secondary to cardiovascular causes,7,9 does not provide any clues as to the underlying mechanism
of protection. From the data available in animal studies, arterial vasodilatation, reduction in myocardial infarct size, and thus reduced progression to ischaemic heart failure are likely contributors. In addition, early in vivo data in animal models suggest that PDE5i has antiarrhythmic effects during ischaemia and post-MI.16

With only 14% variance capture, other factors including wide variation in patient awareness, prescribing rules of local health providers, and recognition of the importance of male sexual health by GP prescribers might have a significant impact. Further understanding of the sources and consequences of the variation in their use across GPs may inform how we can optimise the use of PDE5-i, to improve quality of life and health outcomes for men with T2DM, many of whom remain at significantly elevated cardiovascular risk.

5 | CONCLUSION

We have shown that there is a wide variation in the use of PDE5-is. With only 14% variance capture, other factors including wide variation in patient awareness, prescribing rules of local health providers, and recognition of the importance of male sexual health by GP prescribers might have a significant impact. These will be the subject of further work in this area.

DISCLOSURE
No author has any conflict of interest in relation to this research letter.

ORCID
Martin B. Whyte https://orcid.org/0000-0002-2897-2026
Mark Livingston https://orcid.org/0000-0001-6878-0769
Geoff Hackett https://orcid.org/0000-0003-2073-3001
Adrian H. Heald https://orcid.org/0000-0002-9537-4050

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How to cite this article: Stedman M, Whyte MB, Lunt M, et al. The treatment rate of erectile dysfunction (ED) in younger men with type 2 diabetes is up to four times higher than the equivalent non-diabetes population. Int J Clin Pract. 2020;74:e13538. https://doi.org/10.1111/ijcp.13538