

## **Cardiovascular safety of 5 $\alpha$ -reductase inhibitors in people with benign prostatic hyperplasia and type 2 diabetes: a propensity-score matched analysis**

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## **Abstract**

## 7 Aims

8 5α-Reductase inhibitors are prescribed for the treatment of benign prostatic hyperplasia  
9 (BPH) and their use is associated with increased risk of incident type 2 diabetes. This  
10 study assessed the long-term cardiovascular safety of 5α-reductase inhibitors in  
11 comparison with tamsulosin in people with co-existing BPH and type 2 diabetes.

## 12 Methods and results

13 We performed a retrospective, population-based cohort study using Scottish Diabetes  
14 Research Network National Diabetes Dataset (SDRN-NDS) and IQVIA Medical  
15 Research Data (IMRD-UK). BPH patients  $\geq 40$  years with recorded type 2 diabetes  
16 mellitus and  $\geq 2$  prescriptions of 5 $\alpha$ -reductase inhibitors or tamsulosin (2006-2021) were  
17 included. After 1:2 variable ratio propensity score matching, cause-specific Cox  
18 proportional-hazard models were used to compute the hazard ratio (HR) of incident  
19 major adverse cardiovascular events (MACE). A total of 11,969 patients were included  
20 in SDRN-NDS and 16,492 in IMRD-UK, with median follow-up durations of 3.8 (IQR:  
21 1.7-6.8) and 4.8 (2.0-8.3) years, respectively. In SDRN-NDS, the HR of MACE in

1 patients receiving 5 $\alpha$ -reductase inhibitors relative to tamsulosin was 1.15 (95% CI 1.03-  
2 1.30,  $p = 0.007$ ), driven by increased risk for myocardial infarction (MI) (HR 1.20, 1.03-  
3 1.40,  $p = 0.022$ ). This was replicated in IMRD-UK, where HR was 1.26 (1.07-1.47,  $p =$   
4 0.008) for MACE and 1.33 (1.10-1.60,  $p = 0.005$ ) for MI. We did not observe any  
5 increased risks in stroke, cardiovascular death, microvascular complications of diabetes  
6 or faster progression to insulin-based therapies.

## 7 **Conclusions**

8 Our retrospective data from two large cohorts suggest that the risk of MACE may be  
9 increased among patients with type 2 diabetes taking 5 $\alpha$ -reductase inhibitors, potentially  
10 driven by increased risk of MI. This supports careful monitoring of macrovascular  
11 outcomes when prescribing 5 $\alpha$ -reductase inhibitors in this population.

## 12 **Keywords**

13 Prostatic Hyperplasia; Diabetes Mellitus, Type 2; Enzyme Inhibitors; Cardiovascular  
14 Diseases.

15

## 16 **Main text**

### 17 Introduction

18 Benign prostate hyperplasia (BPH) affects more than 50% of men over 50 years.<sup>1</sup> 5 $\alpha$ -  
19 Reductase inhibitors, finasteride and dutasteride, are widely prescribed to manage the  
20 urinary symptoms of BPH.<sup>1</sup> They work by inhibiting the conversion of testosterone to the

1 more potent dihydrotestosterone (DHT) by the 5 $\alpha$ -reductase isozymes and thus  
2 reducing androgen-dependent prostate growth.

3 5 $\alpha$ -Reductases are also present in metabolic tissues such as liver, adipose, and skeletal  
4 muscles.<sup>2</sup> Pharmacological inhibition of 5 $\alpha$ -reductases activities in man increases  
5 susceptibility to metabolic dysfunction, including insulin resistance, increased HbA<sub>1c</sub>,  
6 dyslipidaemia and hepatic lipid accumulation.<sup>2-4</sup> These effects could be plausibly  
7 mediated through suppressed androgen action or modulated metabolism of other  
8 enzyme substrates including glucocorticoids. A population-based cohort study has  
9 linked both finasteride and dutasteride use to increased risk for new-onset type 2  
10 diabetes.<sup>5</sup> Similarly, adverse metabolic phenotypes including diet-induced weight gain,  
11 impaired glucose tolerance, and increased susceptibility to fatty liver disease were  
12 observed in mice lacking 5 $\alpha$ -reductase 1 enzyme (*Srd5a1*<sup>-/-</sup> mice)<sup>6,7</sup> and following  
13 administration of finasteride to obese Zucker rats.<sup>8</sup>

14 People with type 2 diabetes are at a higher risk of developing cardiovascular diseases<sup>9</sup>  
15 and thus this risk may also be increased in men receiving 5 $\alpha$ -reductase inhibitors. The  
16 aim of this study was to retrospectively examine cardiovascular effects of finasteride  
17 and dutasteride use in patients with co-existing BPH and type 2 diabetes.

18 **Methods**

19 **Datasets**

20 This study used data from two large UK cohorts: The Scottish Diabetes Research  
21 Network - National Diabetes Dataset (SDRN-NDS)<sup>10</sup> and IQVIA Medical Research Data  
22 - UK (IMRD-UK).<sup>11</sup> SDRN-NDS contains electronic health records of the Scottish Care

1 Information-Diabetes Collaboration (SCI-Diabetes), which captures over 99% of  
2 diabetes records in Scotland from 2004 onwards.<sup>10</sup> The dataset is linked to hospital  
3 records in the Scottish Morbidity Records (SMR) and death registry in the National  
4 Records of Scotland (NRS). Diagnoses were determined in SDRN-NDS with ICD-10  
5 codes and medical procedures with OPCS-4 codes.

6 IMRD-UK incorporates data from THIN, a *Cegedim* database, and includes longitudinal  
7 GP records of diagnoses, symptoms, biochemistry, and prescription data of  
8 approximately 4.5% of the UK population as of 2021.<sup>11</sup> The data validity and  
9 generalisability have been well recorded.<sup>12</sup> The diagnoses and procedures were  
10 recorded using Read Codes.

### 11 **Study population**

12 Male individuals were identified from both datasets if they received  $\geq 2$  prescriptions of  
13 finasteride, dutasteride, or tamsulosin between 1 January 2006 and 30 November 2021.  
14 Patients with a diagnosis of type 1 diabetes, alopecia, renal or ureteric calculi, prostate  
15 cancer, or any record of prostate surgery were excluded.

16 For each cohort, eligible patients were divided into three groups: finasteride,  
17 dutasteride, and tamsulosin (control). Patients who initiated finasteride or dutasteride,  
18 either as monotherapy or in combination with tamsulosin, were assigned to the  
19 corresponding 5 $\alpha$ -reductase inhibitors group, according to an intention-to-treat analysis  
20 framework. Given the small number of patients receiving dutasteride, patients  
21 prescribed either finasteride or dutasteride were grouped into a “5 $\alpha$ -reductase inhibitors  
22 (5ARI)” cohort. The effect of individual drug was evaluated in the subgroup analysis.

1 For each patient, the second prescription date of finasteride, dutasteride or tamsulosin  
2 was defined as the index date. Individuals were eligible if they were  $\geq 40$  years and had  
3 remained in the dataset for more than 1 year at the index date.

4 ***Clinical characteristics***

5 Baseline covariates extracted in the SDRN-NDS included: age; duration of diabetes;  
6 social deprivation measured with Scottish index of multiple deprivation<sup>13</sup>; BMI  
7 categories; calendar year at index date; diagnoses of chronic obstructive pulmonary  
8 disease (COPD) and cancer (excluding prostate cancer) prior to the index date; mean  
9 arterial blood pressure; total cholesterol and non-HDL two years prior to the index date;  
10 use of ACE inhibitors, angiotensin-receptor blockers, beta blockers, calcium channel  
11 blockers, diuretics, statins, oral glucocorticoids, glucose-lowering medications, and  
12 nonsteroidal anti-inflammatory drugs (as classified in British National Formulary) one  
13 year prior to the index date. As self-reported ethnicity data and HbA<sub>1c</sub> were only  
14 available for a subset of patients, they were not included during matching and we  
15 considered their balance after matching to reflect residual unmeasured confounding  
16 among groups.<sup>14</sup> Given the low proportion of patients with baseline exposure of  
17 glucose-lowering agents (DPP-4 inhibitors, SGLT2 inhibitors and GLP-1 receptor  
18 agonists), the use of any glucose-lowering medication was included as a covariate  
19 during matching, and balance of number and type of diabetes medications were  
20 assessed after matching.

21 In IMRD-UK, the covariates included age, calendar year, duration of diabetes, number  
22 of GP visits in the past year, Townsend deprivation score,<sup>15</sup> BMI categories, smoking  
23 status, and alcohol consumption, previous diagnoses of COPD, cancer, hypertension,

1 and dyslipidaemia, and use of medications as above. HbA<sub>1c</sub> was not routinely recorded  
2 and ethnicity not captured at individual level within IMRD-UK.

3 **Study outcomes**

4 In SDRN-NDS, the primary outcome included incident major adverse cardiovascular  
5 events (MACE), defined as cardiovascular death, non-fatal myocardial infarction (MI) or  
6 non-fatal ischemic stroke (ICD-10 codes: cardiovascular death, I20-23 and I60-64; MI,  
7 I21; and stroke I63). Secondary outcomes included individual components of MACE,  
8 peripheral vascular disease (ICD-10 codes: E11.5, I70.2, I73., I74.2-9, I79.2);  
9 nephropathy (the earliest record of 2 consecutive readings of eGFR < 30 ml/min/1.73m<sup>2</sup>  
10 more than 90 days apart, derived from MDRD equations); background (R1-4, M1-2) and  
11 referable (R3-4, M2) diabetic eye diseases; diabetic neuropathy (absent of sensation in  
12 monofilament test); and first receipt of insulin-based medications. All secondary  
13 outcomes were incident events, and patients with the outcome at baseline were  
14 excluded from the corresponding analysis.

15 As cause of death was not captured in IMRD-UK, incident MACE was defined as first  
16 occurrence of fatal and non-fatal MI or ischemic stroke. Secondary outcomes included  
17 individual components of MACE and receipt of insulin-based medications.

18 All patients were followed up until the occurrence of outcome of interest, death, end of  
19 registration, or end of the study period on 30 November 2021, whichever came first.

20 **Statistical analysis**

21 Propensity score matching was used to adjust for baseline confounding between  
22 groups. The propensity score was calculated using logistic regression conditioned on

1 baseline covariates as listed above. The exposed patients were matched without  
2 replacement at 1:2 variable ratio to controls within  $\pm 0.05$  calliper of the propensity  
3 score.<sup>16</sup> Extreme values (BMI <13 kg/m<sup>2</sup> or >100 kg/m<sup>2</sup>) were truncated. Missing data  
4 were grouped as the “Missing” category during matching. Balance of covariates after  
5 matching was checked with SMD.  
6 Baseline characteristics of each group were summarized with descriptive statistics and  
7 difference between groups with standardized mean difference (SMD). Incidence rates  
8 were calculated as the number of newly diagnosed patients per 10,000 person years  
9 with 95% Poisson confidence intervals. Cause-specific Cox proportional hazard models  
10 were conducted to calculate the hazard ratio (HR) and 95% confidence intervals  
11 between groups. The proportionality assumptions were checked by plotting Schoenfeld  
12 residuals. Kaplan Meier curve and log-rank tests were used to compare the outcomes  
13 among groups.

#### 14 **Sensitivity analyses**

15 A number of sensitivity analyses were performed to ensure the robustness of results. In  
16 2014, the National Institute for Health and Care Excellence (NICE) recommended  
17 adding a 5 $\alpha$ -reductase inhibitor to  $\alpha$ -blockers as the second-line treatment for BPH.  
18 Therefore, those patients receiving both 5 $\alpha$ -reductase inhibitor and tamsulosin were  
19 included in the main analysis, consistent with the changes in clinical practice guidelines.  
20 Further, to overcome the potential lead-time bias, a sensitivity analysis was performed  
21 using an “Only” cohort where patients were only ever administered finasteride or  
22 dutasteride alone, without tamsulosin. Secondly, to account for the significant reduction  
23 in admissions and diagnoses of cardiovascular diseases during the Covid-19

1 lockdown,<sup>17</sup> the study period was limited from 1 January 2006 to 29 February 2020. A  
2 competing risk analysis was also conducted for primary endpoints using Fine-Gray  
3 method with non-cardiovascular death (SDRN-NDS) and all-cause mortality (IMRD-UK)  
4 as competing events.

5 ***Subgroup and secondary analyses***

6 The individual effect of finasteride and dutasteride was evaluated in the subgroup  
7 analysis and patients co-prescribed finasteride and dutasteride were characterized  
8 according to the first prescription. Propensity score matching was performed separately  
9 with tamsulosin for finasteride and dutasteride groups. In IMRD-UK, we also performed  
10 a secondary analysis in all patients with BPH, where diagnosis of type 2 diabetes was  
11 considered as a binary covariate during matching. All analysis was conducted using R  
12 (version 4.2.2, R Foundation for Statistical Computing, Vienna, Austria).

13

14 **Results**

15 ***Baseline characteristics***

16 Within SDRN-NDS, 36,415 patients received more than one prescription of finasteride,  
17 dutasteride or tamsulosin between January 2006 and November 2021, and 14,687  
18 fulfilled the inclusion criteria (Supplementary Table 1). A total of 11,969 patients were  
19 included after propensity score matching, which included 5,768 patients in the 5ARI  
20 group and 6,201 tamsulosin (Figure 1). Their baseline characteristics were included in  
21 Table 1. Variables were balanced after matching except baseline age between 5ARI  
22 (72.4 years) and tamsulosin (71.0 years) users ( $SMD = 0.150$ ), which was caused by

1 variable ratio matching. We assessed the baseline characteristics with the first-level  
2 matches and covariates were well-balanced (Supplementary Table 2).

3 In IMRD-UK, 17,298 patients fulfilled the selection criteria (Supplementary table 3). The  
4 matched cohort included 16,492 patients, of which 7,165 were in the 5ARI group and  
5 9,327 tamsulosin. Similarly, variables were balanced after matching (Table 2).

## 6 **Use of 5ARI and cardiovascular events**

7 In SDRN-NDS, a total of 1,099 episodes of MACE were recorded over a median follow-  
8 up of 3.8 (IQR: 1.7-6.8) years, of which there were 573 in the 5ARI group and 526 in  
9 tamsulosin (Supplementary table 4). The incidence rate for MACE was 212.0 per  
10 10,000 person years (95% CI: 194.7-229.4) for the 5ARI group, and 191.8 (175.4-208.2)  
11 for tamsulosin. Similarly, in IMRD-UK, the incidence rate for MACE was higher for the  
12 5ARI group (75.4 per 10,000 person-years, 95% CI: 66.9-83.9) when compared to  
13 tamsulosin (61.7, 95% CI: 54.8-68.6). Figure 2 shows the increased probability of  
14 incident MACE among patients in the 5ARI group in both cohorts. This increase was  
15 also observed in all individual components of MACE in both datasets. The cumulative  
16 incidence plots of all individual components of MACE are shown in Supplementary  
17 Figure 1 and 2.

18 Figure 3 shows the results of all estimated Cox proportional hazard models. In SDRN-  
19 NDS, there was an increased risk of MACE, MI, and stroke, but not cardiovascular  
20 death among users of 5 $\alpha$ -reductase inhibitors before propensity score matching. In the  
21 matched cohort, the hazard ratio of MACE is 1.15 (95% CI 1.03-1.30, p = 0.007) for  
22 5ARI when compared to tamsulosin. An increase in risk was observed for incidence MI

1 (HR 1.20, 95% CI 1.03-1.40,  $p = 0.022$ ), but not stroke (HR 1.20, 95% CI 0.98-1.47,  $p =$   
2 0.12) or cardiovascular death (HR 0.89, 95% CI 0.68-1.15,  $p = 0.19$ ). Among secondary  
3 endpoints, the HR for peripheral vascular diseases was 1.20 (95% CI 1.00-1.43,  $p =$   
4 0.047). We did not observe increase in risk for any other microvascular endpoints  
5 including diabetic nephropathy, background or referable eye diseases, or neuropathy.  
6 These findings were replicated in IMRD-UK, where there was an increased risk for  
7 incident MACE in the 5ARI group (HR 1.26, 95% CI 1.07-1.47,  $p = 0.008$ ). This was  
8 again driven by MI where the HR is 1.33 (95% CI 1.10-1.60,  $p = 0.005$ ). The HR for  
9 stroke was 1.12 (95% CI 0.84-1.51,  $p = 0.54$ ). A small decrease in risk for time-to-  
10 receipt of insulin-based therapy was found in SDRN-NDS (HR 0.82, 95% CI 0.72-0.94,  
11  $p = 0.007$ ). However, this was not replicated in IMRD-UK, where the HR was 0.97 (95%  
12 CI 0.86-1.10,  $p = 0.66$ ).

13 The results of the sensitivity analyses testing for effect of Covid-19, the “Only” group,  
14 and the competing risk analysis are shown in Supplementary Tables 5-7. The analyses  
15 were consistent with the primary analyses except the “Only” group in IMRD-UK which  
16 were underpowered due to the low sample size (Supplementary Tables 8).

## 17 **Use of finasteride, dutasteride and cardiovascular events**

18 The individual effect of finasteride or dutasteride was evaluated in subgroup analyses.  
19 For finasteride, a total of 11,891 patients (5,730 in the finasteride group and 6,161  
20 matched tamsulosin) were included in SDRN-NDS and 14,703 (5,763 finasteride and  
21 8,940 matched tamsulosin) in IMRD-UK, respectively. In SDRN-NDS, the HR of  
22 finasteride group was 1.14 (1.01-1.28,  $p = 0.04$ ) for incident MACE, 1.19 (1.02-1.39,  $p =$   
23 0.03) for non-fatal MI, 1.23 (1.01-1.51,  $p = 0.04$ ) for non-fatal stroke, and 0.93 (0.71-

1 1.21,  $p = 0.64$ ) for cardiovascular death. An increase in risk was found for incident  
2 peripheral vascular disease (HR 1.25, 1.04-1.49,  $p = 0.01$ ) but not any other  
3 microvascular complications. In IMRD-UK, the HR was 1.14 (0.97-1.33,  $p = 0.11$ ) for  
4 MACE, 1.21 (1.00-1.45,  $p = 0.05$ ) for MI, and 1.00 (0.74-1.34,  $p = 0.89$ ) for stroke. We  
5 did not observe any increase in risk for faster time to receipt of insulin-based therapy in  
6 either dataset (Supplementary Figure 3).

7 The number of patients prescribed dutasteride was low in both datasets, with 2,155  
8 patients in SDRN-NDS (724 dutasteride and 1,431 matched tamsulosin) and 4,455 in  
9 IMRD-UK (1,488 dutasteride and 2,967 matched tamsulosin). The HR was 0.90 (0.71-  
10 1.16,  $p = 0.72$ ) for MACE in SDRN-NDS, with statistically insignificant results for all  
11 individual components. While in IMRD-UK, the risk increase in the dutasteride group  
12 was higher than finasteride, when compared with tamsulosin. Here the HR was 1.35  
13 (1.02-1.79,  $p = 0.01$ ) for MACE, 1.48 (1.07-2.05,  $p = 0.01$ ) for MI, and 1.08 (0.64-1.82,  $p$   
14 = 0.98) for stroke (Supplementary Figure 4). Similar to the main analysis, a small  
15 decrease in risk for receipt of insulin was found in SDRN-NDS (HR 0.66, 0.48-0.90,  $p =$   
16 0.01), and this was not replicated in the IMRD-UK (HR 1.07, 0.85-1.35,  $p = 0.88$ ).

## 17 **Secondary analysis**

18 In IMRD-UK, a secondary analysis was performed in all patients prescribed 5ARIs or  
19 tamsulosin for BPH between 2006 and 2021, regardless of their diabetes status at  
20 baseline. A total of 110,185 patients fulfilled the inclusion criteria and 102,967 were  
21 included after matching over a median follow-up of 5.7 (IQR: 2.4-9.3) years. This  
22 included 44,809 patients in the 5ARI group and 58,158 in the matched tamsulosin group

1 (Supplementary Table 9). Pre-existing type 2 diabetes was included as an additional  
2 covariate during matching.  
3 The results were consistent with the primary analysis (Figure 4; Supplementary Table  
4 10). The increased risk in MACE was present for the 5ARI group (HR 1.22, 1.13-1.31, p  
5 < 0.001), and separately for finasteride (HR 1.17, 1.09-1.26, p < 0.001), and dutasteride  
6 (HR 1.17, 1.02-1.33, p = 0.006). This was again mainly driven by MI, where the HR was  
7 1.25 (1.15-1.36, p < 0.001) for 5ARI group, 1.19 (1.10-1.30, p < 0.001) for finasteride,  
8 and 1.23 (1.06-1.43, p = 0.02) for dutasteride.

9

10 **Discussion**

11 In this study, we built upon our previous work demonstrating the increased risk of type 2  
12 diabetes following use of 5 $\alpha$ -reductase inhibitors,<sup>5</sup> against the setting that patients with  
13 type 2 diabetes are highly susceptible to cardiovascular complications. We examined  
14 cardiovascular outcomes of 5 $\alpha$ -reductase inhibitors in SDRN-NDS, a dataset with  
15 populational coverage of people living with diabetes in Scotland, and IMRD-UK, where  
16 patients with type 2 diabetes were followed in a primary care setting. In both datasets,  
17 we observed an increased risk of developing incident MACE among users of 5 $\alpha$ -  
18 reductase inhibitors, primarily driven by increased risk of incident myocardial infarction,  
19 when controlling for age and other confounding factors. This increased risk was also  
20 present in all patients prescribed 5 $\alpha$ -reductase inhibitors for BPH, regardless of their  
21 diabetes status at drug initiation. We did not observe increased risk of ischaemic stroke,  
22 cardiovascular death, microvascular complications of diabetes, or reduction in time to

1 receipt of insulin-based therapy. These findings underscore the importance of  
2 monitoring the long-term cardiovascular safety profile in individuals prescribed those  
3 medications.

4

5 In this study, we used an active comparator design with BPH patients prescribed  
6 tamsulosin as controls. Several  $\alpha$ -blockers are licensed in the UK for the management  
7 of lower urinary tract symptoms associated with BPH, including alfuzosin, doxazosin,  
8 prazosin, tamsulosin and terazosin. They work by antagonising  $\alpha_1$ -adrenergic receptors  
9 on smooth muscle cells, where the  $\alpha_1A$  receptor subtype is the most predominant  
10 subtype in human prostate, bladder neck, and urethra.<sup>18</sup> Tamsulosin was selected in our  
11 study as it is the most widely prescribed uroselective  $\alpha$ -blocker in BPH, while non-  
12 selective  $\alpha$ -blockers (doxazosin, prazosin and terazosin) are also prescribed for  
13 hypertension.<sup>19 20</sup> Tamsulosin displayed high affinity for the  $\alpha_1A$  receptor subtype,  
14 resulting in its greater uroselectivity and therefore less potential for adverse  
15 cardiovascular effects.<sup>21 22</sup> Propensity score matching was used to balance the  
16 demographic and clinical covariates between patients in the 5ARI and tamsulosin  
17 groups. Baseline HbA<sub>1c</sub> and the type of glucose-lowering medications were not included  
18 in the matching process, though they were balanced in the matched cohort.

19

20 While BPH remains the most common indication for 5 $\alpha$ -reductase inhibitors  
21 prescriptions, both drugs are sometimes used in the treatment of alopecia, and also for  
22 prostate cancer and hirsutism (albeit unlicensed in the UK). Thus, patients with any

1 record of those indications other than BPH were excluded to maintain a homogenous  
2 study population. Similarly, we excluded patients with renal or ureteric calculi where use  
3 of tamsulosin was indicated recently.<sup>23</sup> We also excluded patients who had undergone  
4 surgical intervention for BPH, as they would not require further symptom-control  
5 medications after the surgery. In both IMRD-UK and SDRN-NDS, we observed an  
6 interesting temporal trend in the use of dutasteride, where prescription numbers have  
7 been decreasing since early 2010s (Supplementary Figure 5). This might be explained  
8 by finasteride coming off label around that time. To account for these changes in clinical  
9 practice, we used calendar year as a covariate in the multivariable model. Due to  
10 numbers of dutasteride users being low in some settings, we grouped both finasteride  
11 and dutasteride into a “5ARI group” to investigate the effect of drug class.

12

13 There are a few limitations to consider. First of all, as of all retrospective population-  
14 based studies, bias may arise from the accuracy and completeness of available  
15 diagnosis and prescriptions records. There was a notable difference between incidence  
16 of cardiovascular diseases between the Scottish and English cohorts (incidence of MI in  
17 finasteride users: 131.5 and 71.7 per 10,000 person years, respectively), despite very  
18 similar baseline characteristics. This is generally consistent with incidence rates found in  
19 previous studies.<sup>24 25</sup> The two datasets were collected in different care settings and thus  
20 status was recorded using different coding systems. Diagnoses were obtained from  
21 hospital in-patient records in SDRN-NDS using ICD-10 codes and from primary care  
22 data in IMRD-UK using Read codes. While the validity and generalisability of both  
23 datasets in diabetes and cardiovascular research have been well recorded,<sup>10 12 24</sup>

1 certain macrovascular and microvascular complications of diabetes are managed in  
2 secondary care and may not be robustly captured using primary care Read codes  
3 alone. For this reason, we studied specific parameters only in the SDRN-NDS which  
4 integrates detailed laboratory tests relevant to diabetes management, diabetic foot  
5 screening outcomes, and retinopathy grading from the SCI-Diabetes.<sup>10</sup> Lastly,  
6 adherence was not measured as the medication record was identified from primary care  
7 records, and the results could only be interpreted under an intention-to-treat framework.  
8 However, we limited the study cohort to patients prescribed more than one prescription  
9 of the study drugs, who were more likely to be long-term users. While our study  
10 provided insights through real-world data, a dedicated prospective study or randomised  
11 controlled trial with longer follow-up would be warranted to validate our observations  
12 and address the potential limitations.

13

14 Previous studies on the cardiovascular safety of 5α-reductase inhibitors have yielded  
15 mixed results. The REDUCE trial found that dutasteride use was associated with  
16 increased risk of composite cardiac failure when compared to placebo,<sup>26</sup> although a  
17 meta-analysis of 12 randomized controlled trials did not find any increased risks of  
18 adverse cardiovascular diseases.<sup>27</sup> In contrast, population-based cohort studies have  
19 reported either no significant difference in hospitalization for heart failure<sup>28</sup> or lowered  
20 risk for incident cardiac failure<sup>29</sup> compared with tamsulosin, though these studies were  
21 indexed at time of BPH diagnosis and thus subjected to prevalent user bias and  
22 immortal time bias.<sup>30</sup> Similarly, a cohort study in Korean men did not report a significant  
23 risk difference in cardiovascular diseases and but instead reduced risk in patients with

1 highest exposure to 5 $\alpha$ -reductase inhibitors,<sup>31</sup> with drug exposure assessed during the  
2 period before the start of follow-up. A previous study also reported reduction in the 1-  
3 year risk of MACE in comparison with tamsulosin although it should be recognized this  
4 follow-up period was short.<sup>32</sup> A nation-wide cohort study in Taiwan reported a lower  
5 cumulative rate of cardiovascular diseases in users of 5 $\alpha$ -reductase inhibitors compared  
6 to tamsulosin.<sup>33</sup> However, it did not adjust for cardiometabolic risk factors such as BMI.  
7 It is important to note that these studies did not specifically focus on people with  
8 diabetes, who might be more susceptible to the long-term cardiovascular consequences  
9 of finasteride or dutasteride.

10

11 The disparity between the link between pharmacological inhibition of 5 $\alpha$ -reductases and  
12 increased risk of myocardial infarction but not ischaemic stroke or microvascular  
13 endpoints was unexpected. While the mechanism underlying this selective risk  
14 difference is unclear, it might be attributed to the distinct aetiologies between MI and  
15 stroke. Most acute MIs are caused by atherosclerotic plaque rupture or erosion, while  
16 causes of acute ischaemic stroke are more heterogeneous.<sup>34-36</sup> There is a strong link  
17 between adverse plasma lipid profiles and MI,<sup>37 38</sup> and long-term dutasteride has been  
18 shown to increase serum total cholesterol and LDL levels.<sup>4</sup> Further research is needed  
19 to investigate whether pharmacological inhibition of 5 $\alpha$ -reductase activities may  
20 selectively influence pathways that are more relevant to MI.

21

1 A number of mechanisms can be proposed to explain the increased cardiometabolic  
2 risks observed. 5 $\alpha$ -Reductases facilitate the A-ring reduction of 3-keto,  $\Delta^{4,5}$  C19/C21  
3 steroids, including cortisol, androgens, progestogens, and mineralocorticoids, all of  
4 which have well recognized effects on energy or vascular homeostasis.<sup>39-42</sup> Alterations  
5 in 5 $\alpha$ -reductase activities may contribute to cardiometabolic dysfunction via  
6 dysregulation of steroid actions, most plausibly through a state of glucocorticoids  
7 excess or androgen deprivation. Glucocorticoids regulate fuel metabolism and increase  
8 the risk of cardiovascular diseases when in excess.<sup>43</sup> 5 $\alpha$ -Reductase deficiency in mice  
9 increases accumulation of glucocorticoids within metabolic tissues such as liver and  
10 adipose,<sup>44</sup> although the propensity to alter risk of plaque development has not been  
11 assessed for example by crossing with *ApoE* deficient mice. Moreover, 5 $\alpha$ -reduced  
12 glucocorticoids retain anti-inflammatory actions, thus depletion of these steroids may  
13 promote vascular inflammation.<sup>45</sup> Similarly, 5 $\alpha$ -reductases converts testosterone to the  
14 most potent androgen DHT and pharmacological inhibition of the enzyme activities  
15 contribute to low circulatory DHT.<sup>2</sup> The adverse metabolic and vascular outcomes of  
16 androgen deficiency in men are well-recorded as seen in men with hypogonadism.<sup>46-47</sup>  
17 In rodents, finasteride induced hepatic steatosis in both castrated and intact mice,  
18 suggesting this adverse metabolic effect might be primarily due to glucocorticoids rather  
19 than androgens.<sup>8</sup> Increased activity of the hypothalamus-pituitary-adrenal (HPA) axis  
20 and impaired negative feedback of cortisol have been reported in people with type 2  
21 diabetes.<sup>48-49-50</sup> Similarly, low serum testosterone levels are also prevalent among men  
22 with type 2 diabetes.<sup>51-52</sup> To our knowledge, there is no direct study available measuring  
23 5 $\alpha$ -reductase activity in people with type 2 diabetes, although increased 5 $\alpha$ -reduction of

1 cortisol has been reported indirectly through urinary metabolite profiling of people with  
2 type 2 diabetes.<sup>53</sup> Future study is warranted to investigate whether synergistic  
3 interactions occur between hypogonadism and 5 $\alpha$ -reductase inhibition, or between  
4 hypercortisolism and 5 $\alpha$ -reductase inhibition (for example, during co-prescription of  
5 synthetic glucocorticoids and 5 $\alpha$ -reductase inhibitors).

6

7 5 $\alpha$ -Reductase inhibitors are also prescribed off-label in women for treatment of  
8 polycystic ovarian syndrome (PCOS) and hirsutism. However, women were not included  
9 in this study due to the low number of patients. Effects of 5 $\alpha$ -reductase inhibitors in  
10 women merits further research as female mice lacking 5 $\alpha$ -reductase 1 enzyme (*Srd5a1*<sup>-</sup>)  
11 were more susceptible to hyperinsulinemia on high fat diet than their male  
12 counterparts,<sup>6</sup> suggesting a potential sexual dimorphism in the magnitude of response  
13 to the drug treatment.

14

## 15 **Conclusion**

16 We have demonstrated that the risk of MACE is increased in BPH patients prescribed  
17 5 $\alpha$ -reductase inhibitors through a propensity-score matched analysis of two UK-based  
18 cohorts. This is driven by an increased risk of incident MI, but not other cardiovascular  
19 outcomes including stroke, cardiovascular death, or microvascular complications of  
20 diabetes. Adverse macrovascular events should be considered as a potential longer  
21 term side effect of 5 $\alpha$ -reductase inhibitors use, especially in patients with existing type 2  
22 diabetes.

1 **Declarations**

2 ***Data availability statement***

3 The data supporting the findings of this study are derived from the SDRN-NDS and  
4 IMRD-UK. Approvals for data linkage and use of data for research purposes for SDRN-  
5 NDS were obtained from the Public Benefit and Privacy Panel for Health and Social  
6 Scare (HSC-PBPP; Reference: 1617-0147) and the West of Scotland Research Ethics  
7 Committee (Reference: 21/WS/0047). Access to SDRN-NDS data is restricted and  
8 available upon reasonable request through the Scottish Diabetes Research Network.  
9 IMRD-UK data are provided by patients as part of routine primary care and are available  
10 upon application to IQVIA's Scientific Research Committee (SRC Reference Number:  
11 21SRC006).

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15 ***Conflict of interest***

16 The authors declare no conflicts of interest.

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20 conceptualization, design, data collection, analysis, decision to publish, or preparation  
21 of the manuscript.

## 1 **Figure legends**

2 **Figure 1:** Consort diagram illustrating the study selection process in (A) SDRN-NDS

3 and (B) diabetic cohort in the IMRD-UK. Abbreviations: 5ARI, 5 $\alpha$ -reductase inhibitors.

4 **Figure 2:** Cumulative incidence plot of major adverse cardiovascular events (MACE) in

5 the propensity score-matched (A) SDRN-NDS and (B) diabetic cohort in IMRD-UK.

6 Abbreviations: 5ARI, 5 $\alpha$ -reductase inhibitors.

7 **Figure 3:** Hazard ratio (HR) and 95% confidence interval for all outcomes in (A) SDRN-

8 NDS and (B) diabetic cohort in IMRD-UK. Major adverse cardiovascular events (MACE)

9 were defined as non-fatal myocardial infarction (MI), non-fatal stroke, or cardiovascular

10 death in SDRN-NDS, and fatal or non-fatal MI and stroke in IMRD-UK.

11 **Figure 4:** Hazard ratio (HR) and 95% confidence interval for all outcomes in general

12 BPH population in the IMRD-UK. Major adverse cardiovascular events (MACE) were

13 defined as fatal or non-fatal MI and stroke in IMRD-UK.

14

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24

25 **Table 1. Baseline characteristics of 5α-reductase inhibitors and tamsulosin**  
 26 **groups in the propensity score-matched SDRN-NDS cohort**

	Tamsulosin	5ARI	SMD
<b>N</b>	6201	5768	
<b>Age</b>	71.0 (9.4)	72.4 (8.8)	0.150
<b>Diabetes duration (year)</b>	10.1 (7.5)	10.2 (7.5)	0.022
<b>SIMD quintile</b>			0.044
<b>1 (most deprived)</b>	997 (16.1)	981 (17.0)	
<b>2</b>	1357 (21.9)	1200 (20.8)	
<b>3</b>	1318 (21.3)	1258 (21.8)	
<b>4</b>	1293 (20.9)	1158 (20.1)	
<b>5 (least deprived)</b>	994 (16.0)	960 (16.6)	
<b>Missing</b>	242 (3.9)	211 (3.7)	
<b>BMI categories</b>			0.047
<b>&lt; 25</b>	848 (13.7)	842 (14.6)	
<b>25-30</b>	2247 (36.2)	2165 (37.5)	

> 30	2967 (47.8)	2629 (45.6)	
Missing	139 (2.2)	132 (2.3)	
<b>Smoking</b>			0.038
No	2269 (36.6)	2077 (36.0)	
Former	2949 (47.6)	2839 (49.2)	
Yes	768 (12.4)	664 (11.5)	
Missing	215 (3.5)	188 (3.3)	
<b>Calendar year</b>			0.121
2006	141 (2.3)	128 (2.2)	
2007	123 (2.0)	177 (3.1)	
2008	184 (3.0)	176 (3.1)	
2009	213 (3.4)	226 (3.9)	
2010	348 (5.6)	281 (4.9)	
2011	326 (5.3)	352 (6.1)	
2012	403 (6.5)	408 (7.1)	
2013	428 (6.9)	359 (6.2)	
2014	464 (7.5)	405 (7.0)	
2015	459 (7.4)	430 (7.5)	
2016	525 (8.5)	417 (7.2)	
2017	480 (7.7)	449 (7.8)	
2018	553 (8.9)	561 (9.7)	
2019	504 (8.1)	491 (8.5)	
2020	477 (7.7)	460 (8.0)	
2021	573 (9.2)	448 (7.8)	
<b>COPD</b>	455 (7.3)	474 (8.2)	0.033
<b>Cancer</b>	713 (11.5)	675 (11.7)	0.006
<b>Biochemistry</b>			
<b>Total cholesterol (mmol/L)</b>	4.1 (0.9)	4.1 (0.9)	0.038
<b>Non-HDL (mmol/L)</b>	3.0 (0.9)	2.9 (0.9)	0.045
<b>Mean arterial pressure (mm Hg)</b>	95.6 (8.0)	95.2 (8.0)	0.051
<b>HbA<sub>1c</sub> (mmol/mol)</b>	58.8 (17.1)	56.8 (15.5)	0.121
<b>Medications</b>			
<b>ACE inhibitors</b>	3067 (49.5)	2852 (49.4)	<0.001
<b>ARB</b>	1111 (17.9)	1041 (18.0)	0.003
<b>Beta-blockers</b>	2103 (33.9)	1987 (34.4)	0.011
<b>Calcium channel blockers</b>	2303 (37.1)	2174 (37.7)	0.011
<b>Diuretics</b>	2124 (34.3)	2042 (35.4)	0.024
<b>Statins</b>	4876 (78.6)	4552 (78.9)	0.007
<b>Oral glucocorticoids</b>	879 (14.2)	834 (14.5)	0.004
<b>NSAID</b>	1765 (28.5)	1657 (28.7)	0.006
<b>Glucose-lowering medications</b>			
<b>Metformin</b>	3888 (62.7)	3481 (60.4)	0.048
<b>Sulfonylurea</b>	1997 (32.2)	1771 (30.7)	0.032
<b>DPP4 inhibitor</b>	668 (10.8)	589 (10.2)	0.018
<b>SGLT2 inhibitor</b>	362 (5.8)	251 (4.4)	0.068
<b>GLP-1 RA</b>	195 (3.1)	154 (2.7)	0.028

<b>Number of glucose-lowering medications</b>			0.061
0	1614 (26.0)	1557 (27.0)	
1	2038 (32.9)	1977 (34.3)	
2	1438 (23.2)	1340 (23.2)	
3	661 (10.7)	577 (10.0)	
3+	450 (7.3)	317 (5.3)	
<b>Number of drugs</b>	1.43 (1.25)	1.35 (1.20)	0.079

1  
2 Data represented in N (%) or mean (SD). Standardized mean difference (SMD)  
3 calculated with reference to tamsulosin group. Abbreviations: 5ARI, 5 $\alpha$ -reductase  
4 inhibitors; SIMD, Scottish index of multiple deprivation; COPD, chronic obstructive  
5 pulmonary disease; ARB, angiotensin II receptor blocker; NSAID, non-steroidal anti-  
6 inflammatory drugs; DPP4, dipeptidyl peptidase-4; SGLT2, sodium-glucose co-  
7 transporter-2 inhibitors; GLP-1 RA, glucagon-like peptide-1 (GLP-1) receptor agonists.  
8

9 **Table 2. Baseline characteristics of 5 $\alpha$ -reductase inhibitors and tamsulosin**  
10 **groups in the propensity score-matched diabetic cohort in IMRD-UK**

	<b>Tamsulosin</b>	<b>5ARI</b>	<b>SMD</b>
<b>N</b>	9327	7165	
<b>Age</b>	71.4 (9.1)	73.4 (8.7)	0.215
<b>GP visits in past year</b>	14.2 (10.4)	14.9 (10.3)	0.065
<b>Diabetes duration (year)</b>	8.8 (6.7)	9.0 (6.9)	0.035
<b>Townsend</b>			0.034
1 (least deprived)	1842 (19.7)	1374 (19.2)	
2	1799 (19.3)	1466 (20.5)	
3	1777 (19.1)	1335 (18.6)	
4	1522 (16.3)	1163 (16.2)	
5 (most deprived)	1052 (11.3)	780 (10.9)	
<b>Missing</b>	1335 (14.3)	1047 (14.6)	
<b>BMI category</b>			0.043
<25	1529 (16.4)	1237 (17.3)	
25-30	3581 (38.4)	2840 (39.6)	
>30	3975 (42.6)	2911 (40.6)	
<b>Missing</b>	242 (2.6)	177 (2.5)	
<b>Smoking</b>			0.043
No	3376 (36.2)	2618 (36.5)	
Former	4938 (52.9)	3861 (53.9)	
Yes	1007 (10.8)	681 (9.5)	
<b>Missing</b>	6 (0.1)	5 (0.1)	
<b>Alcohol consumption</b>			0.015

No	814 (8.7)	610 (8.5)	
Former	1524 (16.3)	1205 (16.8)	
Yes	6705 (71.9)	5140 (71.7)	
Missing	284 (3.0)	210 (2.9)	
Calendar year			0.079
2006	336 (3.6)	299 (4.2)	
2007	362 (3.9)	305 (4.3)	
2008	430 (4.6)	374 (5.2)	
2009	481 (5.2)	417 (5.8)	
2010	657 (7.0)	492 (6.9)	
2011	681 (7.3)	568 (7.9)	
2012	732 (7.8)	578 (8.1)	
2013	794 (8.5)	625 (8.7)	
2014	799 (8.6)	569 (7.9)	
2015	770 (8.3)	545 (7.6)	
2016	659 (7.1)	462 (6.4)	
2017	584 (6.3)	463 (6.5)	
2018	643 (6.9)	451 (6.3)	
2019	591 (6.3)	426 (5.9)	
2020	429 (4.6)	330 (4.6)	
2021	379 (4.1)	261 (3.6)	
COPD	1038 (11.1)	821 (11.5)	0.010
Hypertension	6124 (65.7)	4843 (67.6)	0.041
Dyslipidaemia	2107 (22.6)	1618 (22.6)	<0.001
Cancer	2148 (23.0)	1764 (24.6)	0.037
Baseline medications			
ACE inhibitors	4352 (46.7)	3308 (46.2)	0.010
ARB	1617 (17.3)	1278 (17.8)	0.013
Beta-blockers	2517 (27.0)	2034 (28.4)	0.031
Calcium channel blockers	3260 (35.0)	2517 (35.1)	0.004
Diuretics	2474 (26.5)	2065 (28.8)	0.051
Statins	6916 (74.2)	5325 (74.3)	0.004
Oral glucocorticoids	511 (5.5)	392 (5.5)	<0.001
NSAID	812 (8.7)	558 (7.8)	0.033
Glucose-lowering medications	7116 (76.3)	5304 (74.0)	0.053
Metformin	6347 (68.0)	4602 (64.2)	0.081
Sulfonylurea	2986 (32.0)	2184 (30.5)	0.033
DPP4 inhibitor	1143 (12.3)	827 (11.5)	0.022
SGLT2 inhibitor	332 (3.6)	204 (2.8)	0.040
GLP-1 RA	270 (2.9)	172 (2.4)	0.031
Number of glucose-lowering medications			0.078
0	2065 (22.1)	1750 (24.4)	
1	3585 (38.4)	2836 (39.6)	
2	2556 (27.4)	1805 (25.2)	
3	901 (9.7)	604 (8.4)	

3+	220 (2.4)	170 (2.4)	
<b>Number of drugs</b>	1.32 (1.01)	1.25 (1.00)	0.069

1  
2 Data represented in N (%) or mean (SD). Standardized mean difference (SMD)  
3 calculated with reference to tamsulosin group. Abbreviations: 5ARI, 5 $\alpha$ -reductase  
4 inhibitors; GP, general practice; COPD, chronic obstructive pulmonary disease; ARB,  
5 angiotensin II receptor blocker; NSAID, non-steroidal anti-inflammatory drugs; DPP4,  
6 dipeptidyl peptidase-4; SGLT2, sodium-glucose co-transporter-2 inhibitors; GLP-1 RA,  
7 glucagon-like peptide-1 (GLP-1) receptor agonists.  
8

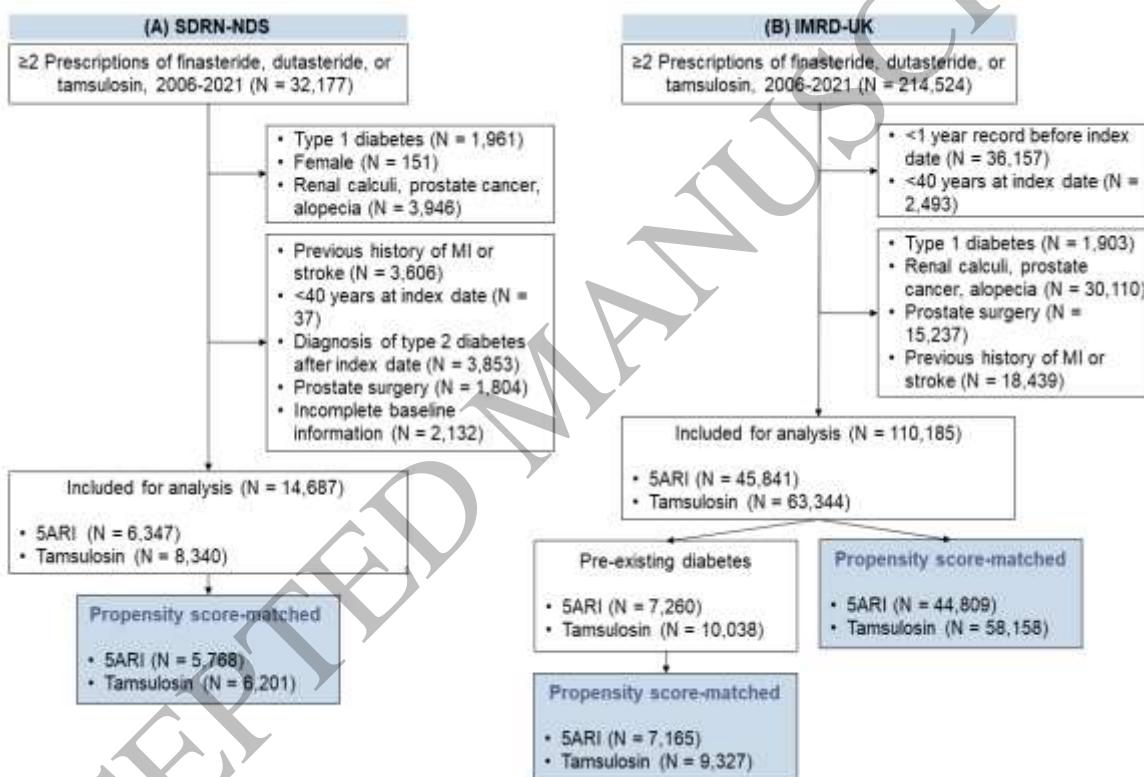


Figure 1  
333x220 mm (x DPI)

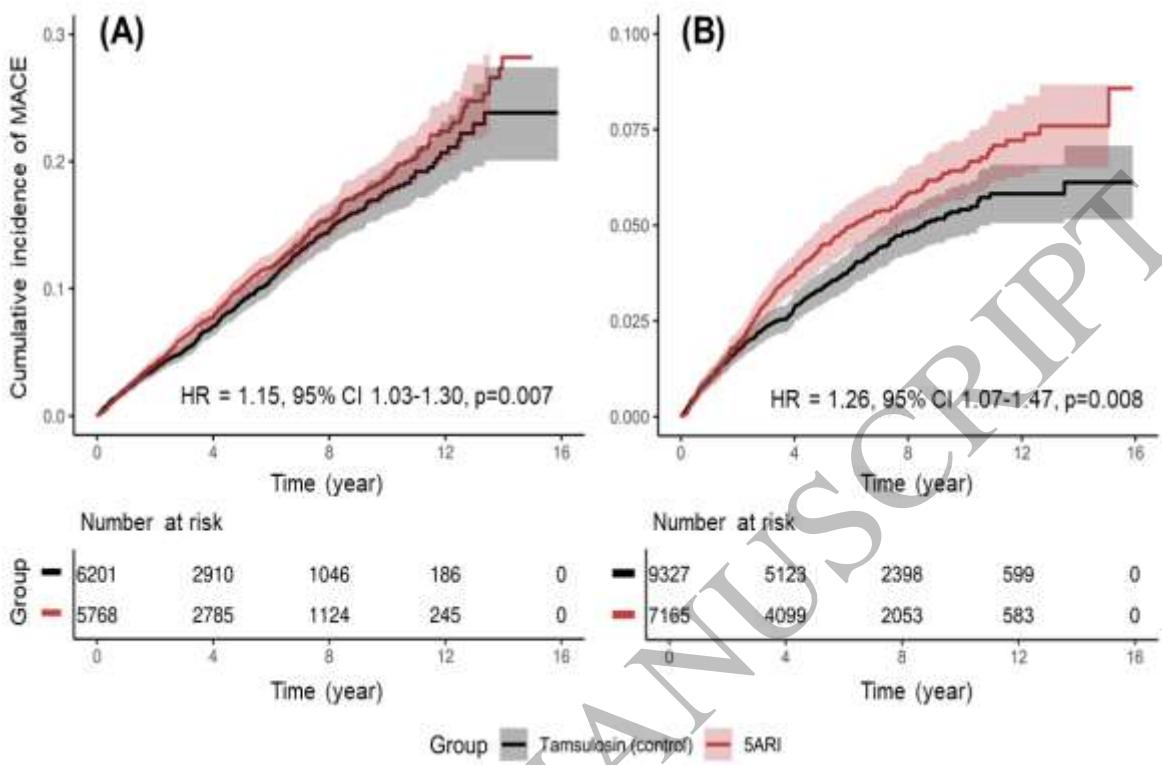


Figure 2  
305x176 mm (x DPI)

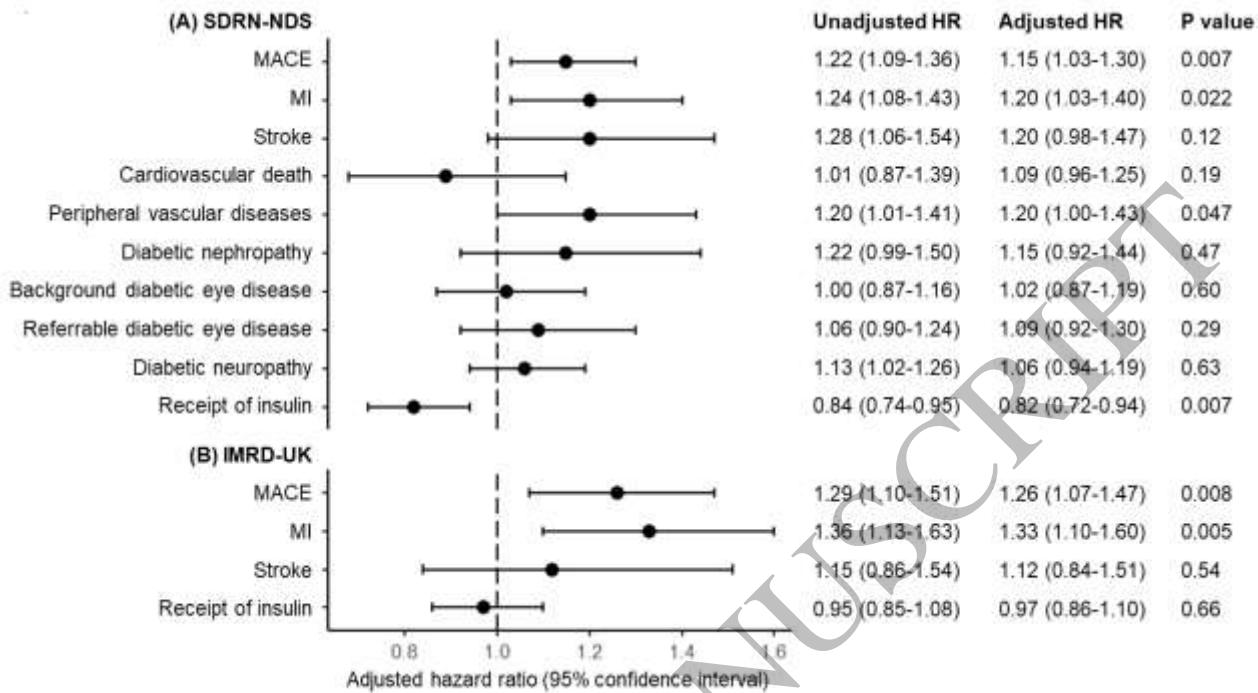


Figure 3  
381x207 mm (x DPI)

1

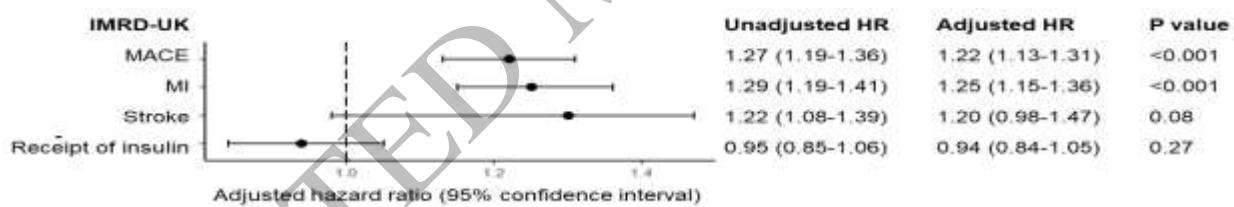
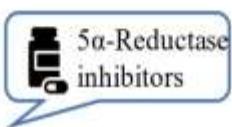


Figure 4  
339x79 mm (x DPI)

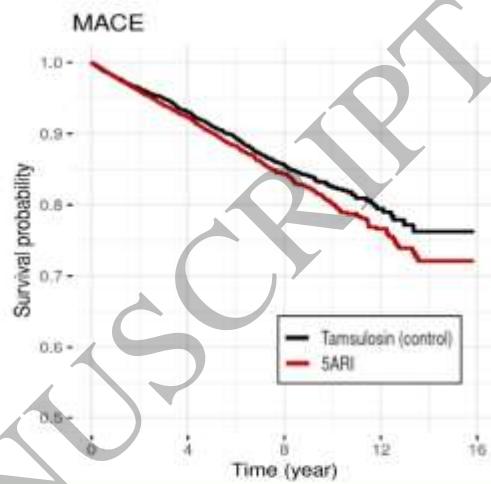
2

## 5 $\alpha$ -reductase inhibitors (5ARI) use and cardiovascular diseases

### Background



### Results



### Methods



- Men  $\geq$  40 years
- BPH and type 2 diabetes
- Received 5ARI or tamsulosin
- 2006-2021

Risk of cardiovascular diseases increased among 5ARI users.

Graphical Abstract

339x190 mm (x DPI)