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Evaluating adverse cardiovascular effects of drug treatment for benign prostatic hyperplasia (BPH): Methodological considerations

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Abstract

When studying the effects of drug exposure in diseases with a long asymptomatic clinical course, exposure classification may be biased by the gradually developing "visibility" of the disease. Benign prostatic hyperplasia (BPH) is such a disease. We found that cardiovascular morbidity is two times more prevalent in patients starting drug treatment for BPH when compared to age-matched population controls. This resulted in a difference of cardiovascular prognostic factors between the exposed and non-exposed. This feature can jeopardize the validity of non-randomized comparisons of drug effects. Moreover, the existence of non-treatment strategies, disease under-reporting, and an elderly population with a high baseline risk of experiencing (cardiovascular) outcome events were encountered as methodological problems. When studying adverse cardiovascular effects in patients using BPH products in a non-randomized fashion, an important question is whether we can measure in the database all relevant prognostic factors and use the information for statistical adjustment. This question is an important challenge to observational research and once again stresses the need for control of possible biases in choosing an appropriate study design.

Keywords: Benign prostatic hyperplasia; Cardiovascular disease; Co-occurrence; Database research; Epidemiologic methods; Bias

1. Introduction

During the last decade, the validity of case–control studies in studying drug effects has been debated frequently in the light of controversies such as the risk of using β-2 adrenoceptor agonists and asthma mortality, risk of myocardial infarction in patients using calcium channel blockers, and risk of venous thromboembolism in women using third generation oral contraceptives. More recently, there was the question whether antihypertensives are associated with cancer [1–4]. Various methodological issues have been identified and debated with respect to studying drug effects in a non-randomized setting, such as confounding by indication, channeling bias, referral and diagnostic bias, and (un)adequate adjustment for exposure variability (duration of use, switching, etc.) [5–8]. Recently, Garbe et al. reported in this journal that random selection of population-based controls in database case–control studies can lead to selection bias [9]. Moreover, they underpinned the problems of selecting and classifying cases and controls in a sample of patients suffering from a disease with a long asymptomatic clinical course, such a glaucoma. In such a sample one may encounter patients with no symptoms, patients with symptoms and no diagnosis, patients with a diagnosis but no treatment and patients with a diagnosis and a treatment. Of course, numerous variations of these scenarios can be expected, posing special problems to the selection of patients in the study.

In this article we continue this subject of studying a disease with a long asymptomatic clinical course. This is done not from the outcome perspective, as Garbe et al. did for glaucoma as an adverse drug effect, but from the exposure perspective. When studying the effects of drug exposure in diseases with a long asymptomatic clinical course, exposure classification may be biased by the gradually developing "visibility" of the disease. Such a disease is benign prostatic hyperplasia (BPH). BPH refers to a histological condition that develops in most aging men from as early as the third decade of life on and can be detected histologically in 90% of

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males by their 80th year of age [10]. Patients with symptomatic BPH suffer from a large set of symptomatic scenarios of lower urinary tract symptoms (LUTS), benign prostatic enlargement (BPE) and bladder outlet obstruction (BOO) [11].

Over the last decade, management of symptomatic BPH has shifted from surgical intervention toward drug therapy. Although transurethral resection of prostatic tissue (TURP) has been shown to be effective, the perception has grown that surgery should be reserved for men with severe symptoms or patients in whom other treatment options have failed [12]. Drug treatment of symptomatic BPH acts on both the mechanical (compression of the urethra by the enlarged prostate) and the dynamical (increased sympathetically controlled smooth muscle tone in the prostate and bladder neck) component of BOO. The mechanical and dynamical components of BOO are treated with 5α-reductase inhibitors and α-adrenoceptor antagonists, respectively. Clinical studies have been shown that both types of drugs improve symptoms and urinary flow rate [13–15].

The study presented in this article was initiated to examine strategies for investigating the association between the use of drugs for the treatment of BPH and the risk of adverse cardiovascular events. The rationale of this risk question has been based upon a number of considerations. There is ongoing caution regarding the use of α-antagonists and the occurrence of adverse effects related to their hemodynamic activity. Although there is only limited evidence from clinical studies, the vasodilatory effects of these drugs can lead to venous pooling, first-dose orthostatic hypotension, and postural orthostatic complaints (dizziness, blurred vision, malaise, asthenia, syncope) [16]. The development of selective α_1-antagonists has reduced the risk of such adverse events compared to non-selective α-blocking agents, but the possibility of cardiovascular side effects remains a relevant pharmacovigilance issue [14,17]. Both the prevalence of BPH and cardiovascular diseases increase with age. Epidemiologic studies exploring co-occurrence of BPH and cardiovascular disease so far have been limited, but estimates for hypertension are that 12–41% of BPH patients have both conditions simultaneously [18,19]. Moreover, the Netherlands Centre for Monitoring of Adverse Reactions to Drugs identified several drugs capable of inducing chest pain and myocardial infarction, including the α_1-adrenoceptor antagonist alfuzosin, used in the treatment of symptomatic BPH [20].

The aim of this study was to compare patients exposed to drugs indicated for use against BPH with patients not using such products. They were compared for the frequency of several cardiovascular risk factors. We also sought to identify methodological considerations when evaluating adverse cardiovascular effects of drug treatment for BPH in an observational setting.

2. Methods

2.1. Study setting

The data used in this study were obtained from the PHARMO-system, a record linkage system including pharmacy dispensing and hospital discharge records of all community-dwelling residents of 8 medium-sized Dutch cities. The PHARMO-system includes over 500,000 patient histories including both detailed information concerning drug use and hospitalizations. For each patient virtually complete historical information is available concerning the type of drug (including excipients), date of dispensing, duration of use, dose regimen and the prescriber as well as the major reason for hospitalization (primary diagnosis), date of admission, duration of hospitalization and all surgical procedures as well as underlying morbidity [21,22]. Because virtually all patients in The Netherlands designate a single pharmacy to fill prescriptions from GPs or medical specialists, dispensing histories provide a complete account of drug exposure in time [23].

2.2 Study design

We compared patients starting BPH drug treatment with an equal number of pharmacy, gender and year of birth matched control patients. From the PHARMO registers we identified men, aged 30 years and older, with a first-ever prescription for a drug, labelled exclusively for the treatment of BPH. BPH products included were the selective α-adrenoceptor antagonists tamsulosin (Omnic®), terazosin, (Hytrin®), alfuzosin (Xatral®) and the 5-α-reductase inhibitor finasteride (Proscar®). The start date of BPH drug exposure was assigned as the index date to the corresponding control. All controls were free from use of any drug labelled for the treatment of BPH. Males with a history of use of non-specific BPH drugs, such as prazosin and doxazosin, were excluded. Both the exposed and non-exposed were eligible for inclusion if they had at least a 1-year history of prescription drug use available before the index date. This criterion was independent of the year of treatment initiation, and therefore not different for patients starting with BPH drugs in 1992 or in 1998.

2.3. Indicators of (cardiovascular) disease: prescription drugs and hospital data

We assessed the general health condition of patients by using the number of drug prescriptions in the year prior to the index date and the Chronic Disease Score (CDS) adapted for the Dutch situation [24]. As indicators for cardiovascular disease, we looked at use of nitrates, calcium channel blockers, cardiac glycosides, ACE inhibitors, diuretics, beta-blockers, antiarrythmics or oral anticoagulants in the year before the index date. Information concerning hospitalizations for cardiovascular indications before BPH treatment initiation was retrieved for an age-stratified sample of 300 first-time users of BPH drugs and 300 controls. Indications for hospital admissions included heart diseases (ICD9CM: 390–459), and in particular acute myocardial infarction (ICD9CM: 410), angina pectoris (ICD9CM: 413), arrhythmias (ICD9CM: 427), congestive heart failure (ICD9CM: 428) and cerebrovascular accidents (IC9CM: 430–438).

2.4. Statistical analysis

We compared cardiovascular risk profiles between the exposed and non-exposed, and between the users of the four different drugs used in BPH treatment. Both conditional and unconditional logistic regression analyses were performed for the estimation of crude and adjusted odds ratios (OR) and 95% confidence intervals (CI) using EGRET.

3. Results

There were 6249 incident BPH drug users identified within the PHARMO database in the period between 1992 and mid-year 1998. Of those patients, 5240 BPH drug users had at least 1 year of prescription drug use available before the index data and were included in the study. Alfuzosin (n = 2744, 52.4%) and finasteride (n = 1211, 23.1%) were the most frequently prescribed drugs, followed by tamsulosin (n = 816, 15.6%) and terazosin (n = 469, 8.9%). Tamsulosin was, however, introduced on the Dutch market not earlier than September 1995, while the other drugs were already available in 1992. Fig. 1 shows the market share of the four main BPH drugs with respect to treatment initiation over calendar time. Before the introduction of tamsulosin, the market was dominated by alfuzosin and finasteride (58% and 33% of all treatment initiations between 1992 and 1994, respectively). Between 1995 and 1996, tamsulosin gained 16% of the market, increasing to 43% of treatment initiations in the period 1997–mid-year 1998, thereby taking over the leading position on the market from alfuzosin. The relative share of finasteride for starting BPH treatment dropped off in time, while the fraction of terazosin starters remained more or less constant over time.

The characteristics of both exposed and non-exposed patients are shown in Table 1. Nearly 70% of the BPH users were 60 years of age or older. Compared to controls, BPH drug users received on average twice as many drug prescriptions in the year before BPH treatment initiation (17.4 versus 8.8 prescriptions per patient, respectively). Calculation of the CDS score for the year prior to the index date showed that patients starting BPH drugs had a poorer health status: 63.4% of the patients had at least one chronic disease, compared to 38.5% for controls. Also, a trend was present over the levels of the CDS score (chi-square test for trend, $P < 0.001$).

Table 2 presents the results for the matched analysis between starters of BPH products and their controls. There was a statistically significant difference in the use of cardiovascular medication in the year before the index date between starters of BPH products and their controls (matched OR 2.0, 95% CI: 1.8–2.2). Stratification for the number of cardiovascular drugs used did not result in odds ratios different from the one found with the dichotomous analysis. A breakdown by type of cardiovascular drug showed statistically significant odds ratios for all drug categories, ranging from 1.3 (95% CI: 1.1–1.6) for lipid lowering drugs to 2.1 (95% CI: 1.5–2.9) for antiarrythmics. The most frequently used cardiovascular drugs among BPH drug users were β-blocking agents (15.3%), diuretics (12.7%) calcium channel blockers (12.3%), ACE inhibitors (11.4%) and nitrates (10.9%).

Fig. 2 displays the history of use of cardiovascular drugs stratified by type of BPH drug. Patients starting with finasteride and tamsulosin had the highest percentage of cardiovascular drug use in the year prior to the start of treatment (45.5% and 43.4%, respectively). For alfuzosin and terazosin, these percentages of recent cardiovascular drug use were 36.0% and 33.9%, respectively. All incident BPH drug users were further stratified as patients starting treatment with tamsulosin (n = 816) and patients starting with any of the other α-blockers (n = 3213). The rationale for this analysis was that tamsulosin had the highest percentage of cardiovascular drug use among the α-blockers and was the drug most recently introduced on the market. The average age of patients starting on tamsulosin was similar compared to users of other α-blockers. There was no difference between both groups with respect to general health score. The age and calendar time adjusted OR for use of cardiovascular medication in the year prior to the index date was 1.4 (95% CI: 1.1–1.7) for tamsulosin users relative to users of other BPH

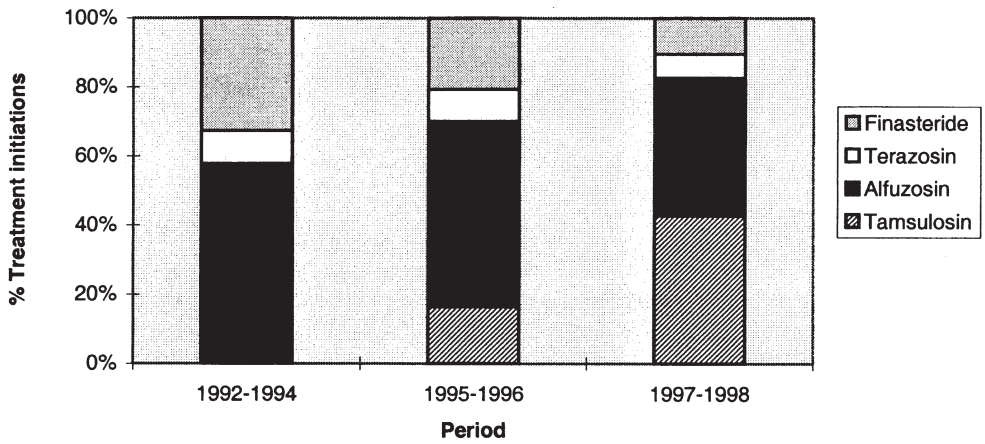

Fig. 1. Treatment initiations of BPH: market share of four main BPH drugs in three periods: 1992–1994, 1995–1996, 1997–mid-year 1998.

Table 1
Descriptive characteristics of the PBH users ($n = 5240$) and matched controls: age distribution; Chronic Disease Score (CDS) and number of prescription drugs used in the year before the index date

Characteristic	BPH user $n = 5240$		Non-BPH user $n = 5240$		Matched odds ratio (95% CI)	
	n	%	*n*	%		
Age group (yrs)						
30–44	289	5.5				
45–59	1368	26.1				
60–74	2493	47.6				
75 and older	1090	20.8				
CDS score						
0	1917	36.6	3220	61.5	1.0	(ref)
1–2	961	18.3	581	11.1	2.8	(2.5-3.2)
3–4	1180	22.5	825	15.7	2.5	(2.3-2.8)
5–6	690	13.2	385	7.3	3.2	(2.8-3.7)
7 or more	492	9.4	229	4.4	4.0	(3.4-4.7)
Total number of prescriptions	91113		46291			
Number per patient	17.4		8.8			

drugs. Evaluation of the number of different cardiovascular drugs taken revealed adjusted ORs of 1.1 (95% CI: 0.9–1.4) for one drug and 1.5 (95% CI: 1.2–1.8) for more than one drug versus none (P-value for trend <0.01). For individual drugs, tamsulosin users were statistically significantly more likely to have a history of use of lipid-lowering drugs (OR 1.5, 95% CI: 1.1–2.0), oral anticoagulants (OR 1.6, 95% CI: 1.2–2.2) and diuretics (OR 1.6, 95% CI: 1.2–2.0).

The number of hospital admissions for cardiovascular indications in a 5-year period before the index date was low. In an age-stratified sample of 300 BPH product users and controls, a total of 34 admissions among BPH product users and 24 among controls were counted. The admissions related to 25 (8.8%) and 18 (6.4%) patients, respectively. These differences were not statistically significant. The number of myocardial infarctions was similar for BPH product users and controls ($n = 9$ in both groups), while there were small differences in the number of hospitalizations for other cardiovascular diases (angina pectoris, arrhytmias, coronary heart failure and cerebrovascular accidents).

Table 2
BPH users and age, gender and pharmacy matched controls ($n = 5240$): cardiovascular prescription drug information in the year before the index date

Use of cardiovascular drugs	BPH user $n = 5240$		Non-BPH user $n = 5240$		Matched odds ratio (95% CI)	
	n	(%)	*n*	(%)		
Use of cardiovascular drugs in year before index date						
Yes	2053	(39.2)	1316	(25.1)	2.0	(1.8–2.2)
Number of cardiovascular drugs used						
None	3187	(60.8)	3924	(74.9)	1.0	(ref)
1 drug	885	(16.9)	553	(10.6)	2.0	(1.8-2.3)
>1 drug	1168	(22.3)	763	(14.6)	2.0	(1.8-2.2)
Specific cardiovascular drugs						
Antiarrythmics	110	(2.1)	54	(1.0)	2.1	(1.5-2.9)
Cardiac glycosides	235	(4.5)	136	(2.6)	1.8	(1.4-2.2)
Calcium channel blockers	646	(12.3)	400	(7.6)	1.7	(1.5-2.0)
ACE inhibitors	595	(11.4)	372	(7.1)	1.7	(1.5-1.9)
Nitrates	571	(10.9)	361	(6.9)	1.7	(1.5-1.9)
Diuretics	667	(12.7)	440	(8.4)	1.6	(1.4-1.9)
β-blocking agents	800	(15.3)	551	(10.5)	1.5	(1.4-1.7)
Oral anticoagulants	422	(8.1)	296	(5.6)	1.5	(1.3-1.7)
Lipid lowering drugs	264	(5.0)	207	(4.0)	1.3	(1.1-1.6)

4. Discussion

Data from this study show that chronic diseases and indicators of cardiovascular disease were more prevalent among patients starting drug treatment for BPH when compared to population controls with the same age. The exposed and non-exposed were thus not comparable for relevant cardiovascular prognostic factors. This finding (i.e., dissimilarities in prognostic factors between treated and non-treated patients for BPH) reflects the same problem as identified by Grobbee and Hoes [5] in the study of Merlo et al. Merlo et al. [25] found an increased risk of MI in patients treated with antihypertensives when compared with those who were not treated. The study of Merlo was classified as being flawed by confounding by indication, as patients treated with antihypertensives do have a different cardiovascular prognosis when compared with patients who are not. Antihypertensives are given to prevent cardiovascular outcomes (e.g., MI, stroke). However, BPH products are not. Thus, although we found an association between BPH treatment and cardiovascular risk factors, this is probably not (only) confounding by indication. Grobbee and Hoes proposed to compare treated with untreated but diagnosed patients. In the case of hypertension that is a feasible approach because hypertension is measured routinely during regular GP visits or health check ups. This is not the case (at least not at the moment) with BPH. In this study, we defined controls as subjects having no history of BPH drug use in the year before the index data and matched on pharmacy and age. A concern regarding the selection of controls is the possibility that patients suffering from BPH symptoms are not seeking medical advice or treatment, or are treated in a different manner (watchful waiting strategy, surgery only), and hence might be misclassified as controls. Patients using BPH products represent only a proportion of all subjects having symptomatic BPH. Stoevelaar reported that the initial treatment choice by urologists ($n = 39$, 13 hospitals, 670 patients) was watchful waiting (41% of all patients), with drug therapy making up 27% [26]. Studies in the Netherlands by Wolfs and Wille-Gussenhoven have indicated that 60–68% of clearly symptomatic men do not seek medical advice, although it must be said that not all of these subjects indeed suffer from BPH [27,28]. On the other hand, Bosch et al. used a number of different criteria for BPH and concluded that the prevalence of symptomatic BPH in the Netherlands

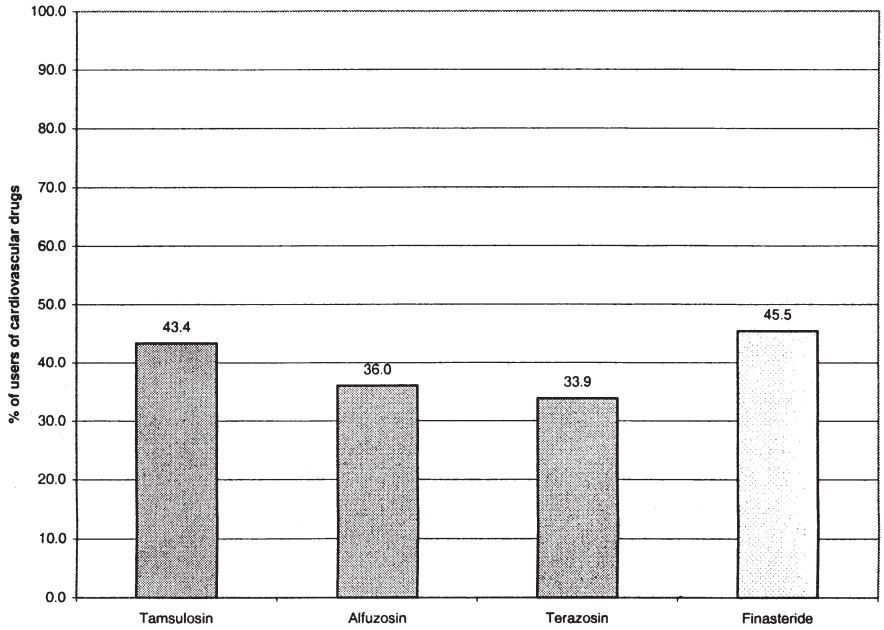

Fig. 2. Proportion of users of cardiovascular drugs in the year prior to the index date among the first-time users of one of the four main BPH products.

does not seem to be over 10% in 55–59-year-old men and 25–30% in 70–74-year-old men [29]. Therefore, the misclassification of controls is probably not a big concern in patients younger than 60 years of age, as the number of non-identified patients make up only 7% of the pool of available controls, making selection of many non-treated, but symptomatic BPH patients in the controls unlikely. Stratification by age category showed that the observed co-occurrence of cardiovascular disease and BPH remained in all four age categories. As the prevalence of BPH increases with age, the chance of selecting controls with undiagnosed or untreated BPH will rise accordingly. Therefore, this finding is reassuring as it shows that co-occurrence is present in the age category with the least chance of misclassification.

In patients over 60 years of age, the issue of misclassification of control is a greater concern. We think that most misclassification will occur for patients on a watchful waiting regime (severity of complaints), and that a contra-indication for the use of BPH products by the presence of cardiovascular disease does not play a relevant part. We performed a sensitivity analysis to estimate the impact of control misclassification on the OR for cardiovascular drug use in the year before the index date. The degree of misclassification of controls is dependent on both the prevalence of symptomatic BPH in the population and the proportion of patients treated with BPH drugs. The percentage of misclassification will increase with a decrease in the percentage of patients treated with BPH products and/or a rise in the prevalence of symptomatic BPH. At a 30% prevalence of symptomatic BPH and assuming that 30% of all patients were treated with BPH products, we found that the odds ratio varied between 1.9 and 2.7 for misclassified controls having a similar cardiovascular drug use pattern as "real" controls, and misclassified controls having a similar cardiovascular drug use pattern as the users of BPH products, respectively (for calculation, see Appendix A).

We found that 39.2% of all starters with BPH products had used cardiovascular drugs in the year prior to the index date. At the start of BPH treatment 31.7% of the patients used cardiovascular drugs concomitantly. This is a higher percentage compared to the results from Lukacs et al., who followed a cohort of French men treated with alfuzosin (n = 5849) in a general practitioner setting for 12 months. Cardiovascular medication was used concomitantly with alfuzosin at baseline in 25.3% of the patients [30]. Michel et al. found in two open labelled observational studies with men with a mean age around 65 years that considerable percentages of BPH drug users had concomitant cardiovascular disease at baseline (23.1% in study 1; 38.4% in study 2) and/or used cardiovascular drugs (i.e., diuretics, β-blockers, calcium antagonists and ACE inhibitors) concomitantly (13.0% and 21.7%) [31]. In this study, 25.8% of all BPH users co-used one of these four drugs. The number of hospitalizations for cardiovascular disease turned out to be low. This suggests that although BPH patients are being treated for concomitant cardiovascular disease, their condition at the time of BPH treatment initiation was probably not so severe that hospitalization was needed.

We used prescription drug information as an indicator for the presence of disease. The indication for the use of prescription drugs was not known, but it seems reasonable that use of specific drugs for the treatment of cardiovascular morbidity is indeed associated with the existence of cardiovascular disease, in particular when combinations are used. Index patients were defined as incident users of drugs, specifically labelled for the treatment of BPH. Prazosin and doxazosin have also been used in the treatment of BPH, but

were developed originally as antihypertensive agents. In order to minimize the risk of selection bias toward cardiovascular risk factors, patients with a history of these drugs were excluded. Terazosin, although indicated for the treatment of BPH, was originally developed as an antihypertensive agent. Exclusion of patients starting BPH treatment with terazosin did not result in different odds ratios, thereby making a bias toward cardiovascular outcomes unlikely.

Another consideration is that the observation of co-occurrence of cardiovascular disease and BPH is due to detection bias. Detection bias can occur if patients experiencing co-morbidity, in this case cardiovascular problems, are more likely to get diagnosed with BPH compared to the more healthy controls. The results of our study show that patients starting BPH drugs have more chronic diseases and prescription drug use and we cannot rule out that such a bias has occurred. Also, the reasons behind the decision to initiate BPH treatment with pharmacotherapy is not known. It is possible that our observation of cardiovascular co-morbidity, is in fact the rationale for the decision to start drug treatment, as opposed to surgery. Co-occurrence of diseases and the use of two or more categories of drug treatment always asks for careful analysis and interpretation because of the question, "what comes first?"

In conclusion, this study shows that cardiovascular morbidity is two times more prevalent in patients starting BPH drug therapy than expected on age, confirming co-occurrence of treated BPH and cardiovascular disease. Potentially, this group of patients can be at a higher risk for adverse effects. Learning more about co-occurring diseases can provide valuable information for identifying patients at an increased risk for adverse outcome events. Also, we identified several methodological problems that can jeopardize the validity of non-randomized comparisons of drug effects. The non-treatment possibility, combined with the under-reporting of LUTS, and an elderly population with a high baseline risk of experiencing cardiovascular outcome events are providing an important challenge for drug safety research. When studying adverse cardiovascular effects in patients using BPH products in a non-randomized fashion, an important question is whether we can measure in the database all relevant prognostic factors and use the information for adjustment in the statistical analysis. This is an important challenge to observational research and once again stresses the need for control of possible biases in choosing an appropriate study design.

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Appendix A. Calculation of the effect of control misclassification for patients aged 60 years and older on the observed odds ratio for use of cardiovascular drugs in the year prior to BPH treatment initiation.

Observed in study:

	BPH+	BPH−	Odds ratio
CV+	1690 (47.2%)	1068 (29.8%)	2.1
CV−	1893	2515	
Total	3583	3583	

CV = cardiovascular drugs.

Prevalence of symptomatic BPH 30%, 30% of patients treated with BPH products. Misclassification of controls = 30% * (100% − 30%) = 21%. Therefore, 0.21 * 3583 = 752 controls are misclassified, 2831 are classified correctly. Assuming that the misclassified controls have a cardiovascular drug use similar to that of the users of BPH products, 752 * 47.2% = 355 CV users.

The adjusted percentage of CV users in the control group is: [1068 − (752*0.472)]/[3,83 − 752] = 25.2%.

This results in the following 2×2 table:

	BPH+	BPH−	Odds ratio
CV+	2045 (47.2%)	713 (25.2%)	2.7
CV−	2290	2118	
Total	4335	2831	