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ORIGINAL ARTICLE

The effects of dutasteride and finasteride on BPH-related hospitalization, surgery and prostate cancer diagnosis: a record-linkage analysis

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Abstract
Purpose To investigate differences in the risk of benign prostatic hyperplasia (BPH)-related hospitalization, for surgical and non-surgical reasons, and of new prostate cancer (PCa) diagnosis between patients using finasteride or dutasteride.
Methods A retrospective cohort study was conducted using data from record linkage of administrative databases (pharmaceutical prescription data, hospital discharge records, Italian population registry). Men aged ≥40 years old who had received a prescription for at least 10 packs/year between January 1, 2004 and December 31, 2004 were included and followed for 5 years.
The association of the outcomes was assessed using a multiple Cox proportional hazard model. Propensity score-matched analysis and a 5–1, greedy 1:1 matching algorithm were performed.
Results 8,132 patients were identified. Overall incidence rates of BPH hospitalization and BPH-related surgery were 21.05 (95 % CI 19.52–22.71) and 20.97 (95 % CI 19.45–22.61) per 1,000 person-years, respectively. In the dutasteride group compared with finasteride group, the incidence rate of both events was statistically significant lower: 16.07 versus 21.76 for BPH hospitalization and 15.91 versus 21.69 for BPH-related surgery. The incidence rate of new PCa was also lower for the dutasteride group [8.34 (95 % CI 5.96–11.68) vs. 10.25 (95 % CI 9.15–11.49)]. Dutasteride was associated with a reduction in BPH-related hospitalizations (HR 0.75, 95 % CI 0.58–0.98 and 0.58–0.98 for surgical and non-surgical reasons). The matched analysis confirmed the risk reduction with dutasteride for BPH-related surgery.
Conclusions These findings suggest that the clinical effects of dutasteride and finasteride might be different. Patients treated with dutasteride seem to be less likely to experience BPH-related hospitalization. Comparative studies are needed to confirm these results.

Keywords Benign prostatic hyperplasia (BPH) · Dutasteride · Finasteride · Epidemiology · Medical record linkage

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Introduction

Lower urinary tract symptoms (LUTS) are common in aging men. There is an increasing understanding that male LUTS result from several pathophysiological conditions. Benign prostatic hyperplasia (BPH) has been recognized as a major contributing factor to the development of LUTS. Because of its high prevalence, the BPH management represents a challenging healthcare issue with economic implications [1]. The first-line pharmacological therapy for men with moderate-to-severe LUTS includes alpha-adrenoreceptor antagonists (ABs) and 5α-reductase inhibitors (5ARIs) alone or in combination [2]. In clinical practice, ABs are used for rapid

symptom relief, while the 5ARIs modify the BPH natural history by delaying the disease progression [3–6]. Finasteride and dutasteride are the two 5ARIs clinically useful. In the prostate tissue, finasteride inhibits the type 2 5-α-reductase isoenzyme, whereas dutasteride inhibits both types (isoenzymes 1 and 2). This dual inhibition results in a greater serum dihydrotestosterone suppression [7]. However, the clinical value of the dual inhibition remains unclear [2]. Several studies have documented the efficacy of treatment with 5ARIs alone or in combination with ABs in the management of BPH [4, 5], but the question of what is, if any, "the best 5ARI" has rarely been addressed in part because comparative data are unavailable or scarce [8–11]. In addition, treatment with 5ARIs has been extensively investigated in order to reduce the incidence of newly detected prostate cancer, but the data, though encouraging, are inconclusive and inconsistent [12, 13]. The issue continues to be the subject of extensive debate within the medical and scientific societies and yet to be determined [14, 15], also considering a potentially different effect between the two drugs [10, 11, 16]. In this context, an observational study on unselected population and in the actual conditions of care can be considered a rich source of clinical information.

Methods and patients

We carried out a retrospective study based on information from three databases: pharmaceutical prescription data, hospital discharge records and Italian population registry. The examined databases include information on approximately 1,500.000 subjects aged ≥40 years. The analysis was performed in 22 Local Health Units between January 1, 2004 and December 31, 2008.

Data sources

The pharmaceutical prescription database documents all prescriptions reimbursed by the National Health System with drugs coded according to the international Anatomical Therapeutic Chemical system (ATC) [17]. The Hospital records include detailed information on primary diagnosis and up to five coexisting diagnoses, procedures performed, and dates of hospital admission and discharge. The diagnoses are classified, according to the International Classification of Diseases-Ninth Revision, Clinical Modification (ICD9-CM) [18]. The Italian population registry provides demographic information (date of birth, sex and date of death if this occurred) on each subject.

A record linkage of these three databases was carried out and pharmacological and clinical history for each patients was obtained. The reliability of this strategy to produce an epidemiological survey has been previously validated and reported [19–21]. All security and protection measures for patient's data were performed according to National laws on privacy protection.

Patients and drugs

The cohort consisted of men aged ≥40 years, who received prescription for at least 10 boxes/year of finasteride or dutasteride in the index year (2004). We have arbitrarily considered the cut off value of 10 boxes/year as reasonable chronic BPH treatment. The first prescription of one of these drugs during the index year was considered as index date (Day 0) for including patient. The exclusion criteria were either exclusive ABs therapy and/or short-term 5-ARI therapy (<10 boxes/year). Dutasteride was commercialized in June 2004, so all patients identified in this year were the new users of this drug. To ensure the same condition for patients treated with finasteride, men who received prescription of this drug in the year preceding the index date were excluded from the cohort. Furthermore, for all patients, the databases were searched during the 12-month period preceding the index date to verify the absence of BPH complications and cancer prostate (PCa). Specifically, patients with an urethral stricture (ICD9-CM: 598, 589.0, 598.00, 598.01, 598.1, 598.2, 598.8, 598.9) and/or with PCa diagnoses (ICD9-CM: 185, 198.82, 233.4, 236.5, 239.5, V10.46) and/or at least a prescription of LHRH analogues and/or antiandrogens were not considered eligible. Patients using ABs (alfuzosin, tamsulosin, terazosin) were included in the study. Moreover, to assess the comorbidities, the Charlson Comorbidity Index (CCI) with the Dartmouth-Manitoba modification was used [22, 23].

Clinical outcomes

Follow-up for each identified patient is extended from the index date to 5 years or until the occurrence of the following major events:

- hospitalization for BPH (non-surgical reasons);
- hospitalization for BPH-related surgery;
- new diagnosis of PCa.

The occurrence of hematuria (ICD9-CM:599.7), bladder stones and diverticula (ICD9-CM:592.0, 592.1, 592.9, 594.1, 563.3), bladder neck obstruction (ICD9-CM:599.7), urinary retention and obstruction (ICD9-CM:788.20, 599.6), acute and chronic renal failure (ICD9-CM:584, 585, 586), hydronephrosis (ICD9-CM:591), urinary infection (ICD9-CM:595.0, 595.4) were also assessed to capture and characterize the "severity factors" in the population.

The new diagnosis of PCa was identified through hospitalization (ICD9-CM:185, 198.82, 233.4, 236.5, 239.5, V10.46) and/or PCa medical therapy (GnRH agonists

L02AE01, L02AE02, L02AE03, L02AE04; and/or antiandrogens: L02BB01, L02BB02, L02BB03).

Statistical analysis

For the whole sample, patients' characteristics were reported as frequency (percentage) and mean ± standard deviation. Differences between patients' treatment subgroups were assessed using standardized difference. For major outcomes, crude incidence rates (IRs) per 1000 men-year were calculated as the number of events divided by the number of person-years of follow-up. Incidence rate ratios (IRRs) with 95 % confidence intervals (CIs) were calculated using Poisson regression model.

The association of hospitalization for BPH, BPH-related surgeryand PCa was assessed using a multiple Cox

Table 1 Patients' characteristics according to the drugs

Before propensity score matching

Variables	Overall (8,132)		Finasteride (7,111)		Dutasteride (1,021)		% Standardized difference[a]
	No.	%	No.	%	No.	%	
Median age (IQR)	73 (66;79)		73 (66;79)		72 (66;78)		
Age (mean, SD)	72.56	(8.95)	72.63	(9.01)	72.07	(8.51)	−6.3901
40–55	272	3.34	245	(3.45)	27	(2.64)	−4.6625
56–65	1,495	18.38	1,293	(18.18)	202	(19.78)	4.0843
66–75	3,213	39.51	2,785	(39.16)	428	(41.92)	5.6135
76–85	2,635	32.40	2,323	(32.67)	312	(30.56)	−4.5379
>85	517	6.36	465	(6.54)	52	(5.09)	−6.1817
Charlson Score							
0	6,947	85.43	6,077	85.46	870	85.21	−0.7027
1–2	756	9.30	659	9.27	97	9.50	0.7996
>=3	429	5.28	375	5.27	54	5.29	0.0689
Previous hospitalization for BPH (non-surgical reasons)	450	5.53	377	5.30	73	7.15	7.6548
Previous BPH-related Surgery	63	0.77	52	0.73	11	1.08	3.6568
Previous BPH complications (severity factors)	259	3.18	221	3.11	38	3.72	3.3812
Previous α-blockers therapy	1,614	19.85	1,483	20.86	131	12.83	−21.566

After propensity score matching

Variables	Finasteride (1,021)		Dutasteride (1,021)		% Standardized difference[a]
	No.	%	No.	%	
Median age (IQR)	72 (66;78)		72 (66;78)		
Age (mean, SD)	72.04	(8.53)	72.07	(8.51)	0.3521
40–55	29	(2.84)	27	(2.64)	−1.1995
56–65	198	(19.39)	202	(19.78)	0.9871
66–75	432	(42.31)	428	(41.92)	−0.7935
76–85	311	(30.46)	312	(30.56)	0.2127
>85	51	(5.00)	52	(5.09)	0.4475
Charlson score					
0	863	84.52	870	85.21	1.91
1–2	104	10.19	97	9.50	−2.30
>=3	54	5.29	54	5.29	0
Previous hospitalization for BPH (non-surgical reasons)	71	6.95	73	7.15	0.76
Previous hospitalization for BPH-related surgery	10	0.98	11	1.08	0.97
Previous BPH complications (severity factors)	36	3.53	38	3.72	1.04
Previous alphablockers therapy	130	12.73	131	12.83	0.29

[a] Standardized difference greater than 10 % represents meaningful imbalance in explored variable between treatment groups

Table 2 Crude incidence rate and incidence rate ratio by outcome considered in overall sample, finasteride and dutasteride groups

Outcome	Overall		Finasteride		Dutasteride		IRR (95 % CI)
	Events	Incidence rate (95 % CI)	Events	Incidence rate (95 % CI)	Events	Incidence rate (95 %CI)	Dutasteride versus finasteride
Hospitalization for BPH	673	21.05 (19.52,22.71)	609	21.76 (20.10,23.56)	64	16.07 (12.58,20.53)	0.74 (0.57,0.96) $p = 0.0210$
Hospitalization for BPH-related surgery	675	20.97 (19.45,22.61)	611	21.69 (20.03,23.48)	64	15.91 (12.45,20.33)	0.73 (0.57,0.95) $p = 0.0183$
Prostate cancer	330	10.02 (8.99,11.16)	296	10.25 (9.15,11.49)	34	8.34 (5.96,11.68)	0.81 (0.57,1.16) $p = 0.2552$

* *E N°* patients with events, *IR* Incidence rate for 1,000 person-years, *IRR* Incidence rate ratio

proportional hazard model. All multivariate analyses were adjusted for the following variables: age, Charlson comorbidity score, previous hospitalization for BPH, previous BPH-related surgery, pre-existing severity factors, previous pharmacological treatment with ABs. Results are expressed as hazard ratios (HRs) and 95 % confidence intervals (CIs).

Furthermore, to check consistency of our results, a propensity score (PS)–matched analysis was performed [24, 25]. A logistic model including the same covariates used in the multivariate Cox model—plus quadratic terms and a set of two-term interactions between the same covariates—was performed to predict the probability to be assigned to study drugs. PS logistic model was selected in a stepwise fashion, and pair-wise comparisons were performed. A 5–1, greedy 1:1 matching algorithm [26] was used to identify a unique matched control for treated patient according to their PS. Adequacy of covariate balance in the matched sample was assessed via standardized difference between the two groups, considering differences less than 10 % as good balance [27].

Finally, since PS methodology addresses only imbalances due to measured confounders, we also performed a sensitivity analysis to account for potential residual confounding deriving from the effect of an unmeasured binary covariate [28].

p values <0.05 were considered significant. All analyses were performed using SAS Statistical Package Release 9.2 (SAS Institute, Cary, NC, USA).

Results

Patients characteristics

From 1,417.969 men aged ≥40 years, 72,943 (5 %) chronically treated with drugs for BPH were identified, without significant variation in prescriptions across the 22 Local Health Units. Among these, 8,132 were chronically exposed to 5ARIs; 7,111 received finasteride and 1,021 dutasteride. No significant differences were observed between these two groups with exception of previous ABs therapy (Table 1).

Clinical outcomes during follow-up

During 5 years, 673 patients were hospitalized for BPH non-surgical reasons, 675 for BPH-related surgery and 330 were newly diagnosed with PCa. The overall hospitalization IR for BPH non-surgical reasons and for BPH-related surgery were 21.05 (95 % CI, 19.52–22.71) and 20.97 (95 % CI, 19.45–22.61) per 1000 person-years, respectively. Among patients under dutasteride compared with those under finasteride, the IR of both events was lower (IRR = 0.74; 95 % CI, 0.57–0.96; for both hospitalizations) (Table 2). For new-onset PCa, the overall IR was 10.02 (95 % CI, 8.99–11.16) per 1000 person-years with no difference between the two drug groups (IRR = 0.81; 95 % CI, 0.57–1.16) (Table 2).

The multivariate analysis showed that dutasteride was associated with an independent reduced likelihood of hospitalization for BPH and for BPH-related surgery (HR 0.75; 95 %CI, 0.58–0.98 and HR 0.75; 95 % CI, 0.58–0.98; $p = 0.03$) and a positive trend, not statistically significant, toward less risk of newly detected PCa (HR 0.81, 95 % CI, 0.57–1.16; $p = 0.24$). The adjusted survival curves of patients under dutasteride and those under finasteride are presented in Fig. 1.

The matched analysis identified 2,042 patients: 1,021 under dutasteride were matched with 1,021 under finasteride. No significant differences were observed among groups (Table 1). The adjusted propensity score–matched Cox model confirmed the positive effect of dutasteride only on hospitalization for BPH-related surgery (HR 0.68, 95 % CI, 0.48–0.96; $p < 0.02$); no significant differences were observed for non-surgical BPH hospitalization (HR 0.76, 95 % CI, 0.54–1.07; $p = 0.11$) and for newly detected PCa (HR 0.78,95 % CI, 0.48–1.27; $p = 0.31$). Moreover, the sensitivity analysis showed that in order to modify the results, an unmeasured confounder should have a hypothetical hazard ratio of at least 1.25 (HR > 1.25) and an

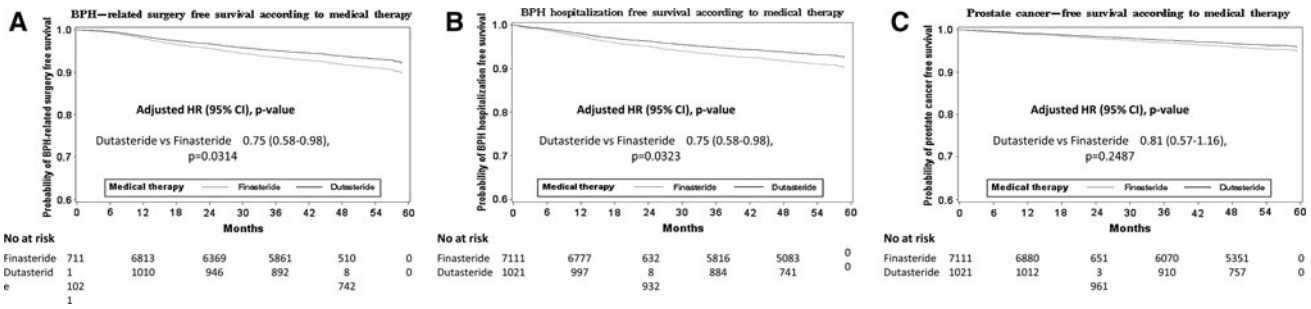

Fig. 1 Event-free according to medical therapy

asymmetrical distribution between finasteride and dutasteride groups of at least 20 % for both the outcomes analyzed (surgical and non-surgical hospitalization).

Discussion

Dutasteride and finasteride are the two currently available 5ARIs and are widely recommended in patients with moderate-to-severe BPH-related LUTS [6]. Their short- and long-term (i.e., >4 years) efficacy and safety profiles have been demonstrated in numerous clinical studies [4, 5].

By blocking both the type-1 and type-2 5α-reductase-isoenzymes, dutasteride achieves 50 % more serum dihydrotestosterone suppression than finasteride. Because it is still not clear whether and to what extent this increased suppression affects the clinical outcomes, a long-term comparative study between the two drugs would be advisable in order to clarify the benefit of the dual 5αR-isoenzymes inhibition.

Placebo-controlled studies have shown reduced rates of acute urinary retention (AUR) and surgical therapy with both 5ARIs. In the PLESS study, after 4 years, finasteride treatment reduced the relative risk of AUR by 57 % and of surgery by 55 % [29]. In the MTOPS study, a significant reduction in the risk of overall clinical progression by 34 % was reported [4]. The COMBAT study also reported lower incidence of AUR in the dutasteride group (2.7 %) compared to the tamsulosin group (6.8 %) [5]. However, a comparative analysis of these results cannot be made, because differences in patient populations and in trial design may have affected the outcomes.

The EPICS study, the only randomized clinical trial comparing dutasteride vs finasteride, did not show significant differences between the drugs in terms of clinical efficacy. However, as pointed out by the authors, the study had two main limitations: the use of prostate volume as surrogate endpoint for AUR and BPH-related surgery and the too short (1-year) duration [11].

In lack of valuable, prospective comparator studies, the purpose of the present study was to assess the likelihood of BPH-related hospitalization, surgery and new detection of PCa in patients under dutasteride or finasteride therapy in a real-world, managed care setting. Even with the well-known limitations of this kind of approach, this study has been conducted because it reflects the real life of prescriptions, clinical uses, and finally physician's attitudes.

In our study cohort, the crude incidence rate of hospitalization for BPH medical reasons and for BPH surgery were 21.7 and 21.6 in the finasteride group and 16.0 and 15.9 in the dutasteride group, respectively. These findings confirm that patients treated with dutasteride are less likely to experience BPH hospitalization and BPH-related surgery than patients treated with finasteride (Fig. 1). Our results are similar to those reported by Issa [10]. The authors, albeit in a smaller population, showed that patients under dutasteride were protected against the AUR risk with a trend toward less prostate-related surgery. In another study, Fenter showed a statistically significant difference in the likelihood of AUR and prostate surgery between dutasteride and finasteride [30], in favor of dutasteride.

Taken together, this evidence supports the clinical benefit of the dual 5α-reductase-isoenzymes inhibition. The two molecules are effective in BPH; nevertheless, due to its peculiar pharmacokynetic and pharmacodynamic characteristics (longer half-life and dual inhibition of 5α-reductase-isoenzymes), dutasteride seems to be more active.

As far as the new diagnosis of PCa is concerned, in our peculiar setting, we found a PCa incidence lower (IR10.03 finasteride group vs IR8.22 dutasteride group) than that reported in the PCPT and REDUCE trials (18.4 and 19.9 %, respectively) [12, 13]. This discrepancy reflects the fact that both trials were conducted in men at risk for PCa (particularly REDUCE), but without a PCa diagnosis at study entry. On the other hand, we analyzed a very large, unselected population typical of observational studies, which better reflects the real-world practice and policy.

Despite the lack of significant differences in PCa detection, we have found a positive trend in favor of dutasteride (HR, 0.81; 95 % CI, 0.57–1.17; $p = 0.25$). This outcome could also reflect the more intense hormonal suppression made by dutasteride and could be verified in a larger sample size with a longer follow-up.

Although our results suggest that there are differences between the two 5ARIs in terms of clinical outcomes, interpretation of the results is limited by the retrospective, non-randomized nature of the study. In fact, we have no information about symptoms scores, uroflowmetry parameters, baseline PSA values, number and kind of biopsies and Gleason score. This is main limitation of the study that hinders any inference about detailed outcomes (such as the subjective burden of the disease and the tumor aggressiveness). However, the administrative database is widely used with all the inherent limitations and is considered a valuable source of clinical information [19–21].

To minimize the influence of selection bias, our analysis was adjusted for several covariates and was also refined by using the propensity score–matched analysis, the matching algorithm and the sensitivity analysis to account for potential residual confounders deriving from the effect of an unmeasured binary covariate.

In conclusion, the comparison of dutasteride and finasteride monotherapies shows that treatment with dutasteride significantly reduces the overall risk of BPH-related surgery hospitalizations. About the risk of PCa development, the effect of dutasteride treatment, as compared to finasteride, shows a positive trend although this did not reach statistical significance. Further clinical trials are warranted in order to evaluate the long-term effectiveness of these drugs.

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Conflict of interest The authors declare that they have no conflict of interest.

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