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Abstract: Objectives: To examine the link between medication use and the risk of bleeding complications following transurethral resection of the prostate from the second postoperative day until hospital discharge. Method: Using a retrospective observational study design, the medical records of all patients who underwent transurethral resection of the prostate over a 24-month period were examined. Comprehensive data regarding patients' medication history, comorbidities and complications that occurred either during or after surgery were collected from medical records. Inferential statistical analysis was used to examine associations between demographic and medication variables and the risk of complications. Results: Complications arising after surgery occurred in 48/135 (36%) of patients. The most common complications postoperatively were haematuria, occurring in 41/48 (85%) and haematuria with clot retention, occurring in 24/48 (50%) of patients who suffered complications. There was a significant association between the number of medications prescribed and postoperative complications; for haematuria, $\chi 2$ (12) = 21.50, p=0.04; and for haematuria with clot retention $\chi 2$ (12) = 24.97, p=0.015. Conclusions: Demographic data relating to patients' age, comorbid state and the number of standard medications prescribed is associated with an increase in macroscopic haematuria and macroscopic haematuria with clot retention after transurethral resection of the prostate. These findings emphasise the importance of nursing practice in both preoperative and postoperative care of patients undergoing surgery. Nurses need to be very vigilant in assessing patients at risk of increased bleeding from a transurethral resection of the prostate by examining their medication regimen.

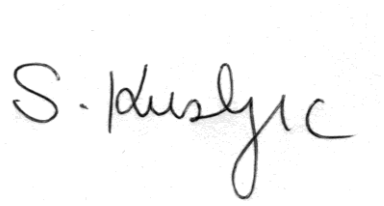
19th June, 2015

Collegian: The Australian Journal of Nursing Practice, Scholarship and Research
Editor-in-Chief
Professor Lisa McKenna

Dear Professor McKenna,

Please find enclosed our final manuscript entitled "Incidence of complications in men undergoing transurethral resection of the prostate". The formatting of journal titles in the reference list has been corrected in accordance with that used in Collegian.

Sincerely,



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Incidence of complications in men undergoing transurethral resection of the prostate

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Comments from the editors and reviewers

Please correct the formatting of journal titles in the reference list in accordance with that used in Collegian.

Response: The formatting of journal titles in the reference list has been corrected in accordance with that used in Collegian. Many thanks for pointing this pout.

Abstract and key words

Objectives: To examine the link between medication use and the risk of bleeding complications following transurethral resection of the prostate from the second postoperative day until hospital discharge.

Method: Using a retrospective observational study design, the medical records of all patients who underwent transurethral resection of the prostate over a 24-month period were examined. Comprehensive data regarding patients' medication history, comorbidities and complications that occurred either during or after surgery were collected from medical records. Inferential statistical analysis was used to examine associations between demographic and medication variables and the risk of complications.

Results: Complications arising after surgery occurred in 48/135 (36%) of patients. The most common complications postoperatively were haematuria, occurring in 41/48 (85%) and haematuria with clot retention, occurring in 24/48 (50%) of patients who suffered complications. There was a significant association between the number of medications prescribed and postoperative complications; for haematuria, χ^2 (12) = 21.50, p=0.04; and for haematuria with clot retention χ^2 (12) = 24.97, p=0.015.

Conclusions: Demographic data relating to patients' age, comorbid state and the number of standard medications prescribed is associated with an increase in macroscopic haematuria and macroscopic haematuria with clot retention after transurethral resection of the prostate. These findings emphasise the importance of nursing practice in both preoperative and postoperative care of patients undergoing surgery. Nurses need to be very vigilant in assessing patients at risk of increased bleeding from a transurethral resection of the prostate by examining their medication regimen.

Key words: ageing, haematuria, medication use, physiological changes, transurethral resection of the prostate

Introduction

Benign prostatic hyperplasia (BPH) and prostate cancer are age-dependent conditions that occur predominantly in men over the age of forty. Both conditions are characterized by formation of large nodules in the prostate gland, which can compress the urethra causing an obstruction that leads to lower urinary tract symptoms (LUTS) (Heidenreich et al., 2013; Oesterling, 1996). LUTS are comprised of obstructive and irrigative symptoms, which can significantly affect the quality of life of older men (Thorpe & Neal, 2003). Despite introduction of pharmacological therapies to relieve LUTS, transurethral resection of the prostate (TURP) remains the gold standard in the management of LUTS (Madersbacher & Marberger, 1999). Despite providing fewer complications than older treatments such as radical prostatectomy, TURP can cause serious short and long-term complications. Common complications include intraoperative and post-operative bleeding, clot retention, urinary tract infection, urethral strictures and bladder neck contractures (Rassweiler, Teber, Kuntz, & Hofmann, 2006).

Moderate postoperative bleeding is the most common complication after TURP which significantly affects patients' recovery, prolonging hospital stay and increasing chances of further complications such as urinary tract infections (Kavanagh, Jack, & Lawrentschuk, 2011). Approximately 25% of patients develop bacteriuria after TURP and therefore antimicrobial therapy is administered perioperatively (Girou, Rioux, Brun-Buisson, & Lobel, 2006). It is however important to emphasize that the severity of complications postoperatively is directly reflective of the medical condition and age of the patients undergoing TURP (Polanczyk et al., 2001; Turrentine, Wang, Simpson, & Jones, 2006). Current evidence shows that the mean age of patients undergoing TURP is 67 years (Mayer, Kroeze, Chopra, Bottle, & Patel, 2012) thus the incidence of co-existing medical conditions or comorbidities is highly prevalent in this group which in turn requires complex pharmacological regimens.

Hypertension is the most common cardiovascular problem amongst the older population followed by arrhythmias and cerebrovascular events such as stroke (Biskupiak, Kim, Phatak, & Wu, 2010; Piccini et al., 2012). Therefore, a high proportion of older people require prescription of multiple medications of which the most common are antihypertensive, antiplatelet and anticoagulant medications. These three medication classes are used to prevent further complications associated with cardiovascular and cerebrovascular disease (Dickerson & Gibson, 2005; Garcia-Rodriguez, Gaist, Morton, Cookson, & Gonzalez-Perez, 2013; Kumar, Calhoun, & Dudenbostel, 2013; Lamberts et al., 2013). Antihypertensive medications act by reducing the blood volume and peripheral resistance, whereas antiplatelet and anticoagulant medications modify the blood clotting mechanisms thus inhibiting the platelet aggregation and thrombus formation (Di Minno, Momi, Di Minno, & Russolillo, 2013; Neutel & Smith, 2013). Patients taking aspirin and warfarin have a higher rate of perioperative bleeding associated with TURP (Taylor, Filgate, Guo, & Macneil, 2011) while patients who had these medications withheld preoperatively have a significantly higher risk of myocardial infarction or stroke.

Current recommendations suggest that when antiplatelet medications are being used for primary prevention, for example, in patients with a family history of cardiovascular and cerebrovascular disease, these medications can be safely withheld preoperatively. However, when these medications are being used for secondary prevention, they should be used without interruption (Chassot, Delabays, & Spahn, 2007). With an increasing number of older patients being prescribed and requiring both anti-platelet and anticoagulant medications, it is a matter of deciding case-by-case whether the risk of ceasing medication is worth the risk of increased bleeding postoperatively. Conversely, there is evidence to show that certain medications such as finasteride are associated with a decreased risk of postoperative bleeding if administered before undergoing a TURP (Donohue, Hayne, Karnik, Thomas, & Foster, 2005). Finasteride is a 5α-

reductase inhibitor that blocks the conversion of testosterone to dihydrotestosterone and as a result of that decreases the activity of androgen-controlled growth factors responsible for angiogenesis and hence leads to reduction in postoperative bleeding (Hagerty, Ginsberg, Harmon, & Harkaway, 2000). Administration of finasteride for two weeks prior to TURP significantly decreased the incidence of perioperative bleeding, thus allowing for a potentially shorter procedure, fewer complications, and reduced hospital stay post-surgery (Donohue et al., 2005).

It is apparent from the literature that patients undergoing TURP are older than 65 years of age and are likely to be on multiple medications due to the various co-existing chronic conditions (Biskupiak et al., 2010; Piccini et al., 2012) thus more susceptible to post-operative complications. Previous studies have demonstrated the link between anticoagulant and antiplatelet therapy and the risk of bleeding during and after TURP. However, no studies have addressed the relationship between other common classes of medications prescribed to older people and complications following TURP. The aim of this study was to examine the link between different medications, which are reflective of the patients' underlying medical conditions such as cardiovascular disease, diabetes mellitus, osteoarthritis and the risk of complications following TURP. Nurses play an important role in monitoring patients' risk of bleeding from a TURP and are the key-providers of hands-on care in these cases. Furthermore, nurses are involved in assessing and evaluating the therapeutic and unwanted effects of medications. Therefore, this research provides important knowledge that could be used to develop strategies to help nurses to carry out their role especially when nursing older people with multiple chronic comorbidities.

Method

Participants and study design

Using a retrospective observational study design, the medical records of patients admitted to a large scale academic hospital in Melbourne, Australia for a TURP were examined. The study population included the whole population of patients who underwent TURP over a 24-month period from January 2011 to December 2012 consisted of 145 patients. The study was approved by the Human Resource Ethics Committee of Melbourne Health, Australia (Ethics approval QA2013051). Comprehensive data regarding patients' medication history, comorbidities and complications that occurred either during or after surgery were collected from medical records. Data were collected using a hard copy of the data collection tool. The following details were documented: age, comorbidities, medications administered pre-operatively and peri-operatively, standard medications taken by a patient and complications following TURP. A standard medication is a medication taken by patients regularly to manage their chronic condition. Different types of complications were recorded by using comprehensive clinical notes. According to the clinical notes, haematuria was assessed through macroscopic evaluation of urine colour from the second postoperative day until hospital discharge. Depending on the amount of blood in urine, the colour of urine changed to rose, red or brown. Furthermore, the clinical notes also recorded the presence of blood clots in the urine based on macroscopic evaluation during the same time-frame (second postoperative day until hospital discharge). Data from 10 patients were excluded from the study due to having incomplete medical records, thus the total number of patients whose medical records were retrieved, was 135.

Statistical analysis

Hard copy data were transferred and stored in a Microsoft Excel spreadsheet. Statistical analysis was performed using the IBM Statistical Package for the Social Sciences (SPSS, Version 21, Chicago, IL, USA). Descriptive statistical analysis was performed on patients' age, number and

type of standard medications prescribed, comorbidities and diagnosis that led to the TURP. Chi-square analysis and Pearson correlation coefficient (r) were used to determine associations between demographic variables and the risk of complications. Furthermore, Chi-square analysis and Pearson correlation coefficient (r) were used to examine associations between explanatory variables and complications following surgery. A p value of 0.05 was considered to be statistically significant. Demographic data are presented as mean and standard deviation (SD).

Results

Demographic characteristics

The mean age of patients was 72.3 years (SD=9.0 years) of age. The youngest patient was 53 whereas the oldest patient was 92 years of age. Of the patients, 116/135 (86%) had one or more comorbidities. Eighty-nine patients or 77% were suffering from one or more cardiovascular diseases with hypertension, ischemic heart disease and atrial fibrillation being the most predominant. Only three patients or 2.6% had suffered from cerebrovascular disease. Forty patients or 35% were suffering from type-2 diabetes mellitus whereas 98 patients or 85% suffered from other comorbidities with hypercholesterolemia, gastroesophageal reflux disease (GORD) and osteoarthritis being the most common (Fig. 1). The main reasons for undergoing TURP were hyperplasia of the prostate and malignant neoplasm of the prostate. Of the patients, 99/135 (73%) were diagnosed with hyperplasia of the prostate. Nine patients or 7% were diagnosed with a malignant neoplasm of the prostate, six or 4% were diagnosed with obstructive and reflux uropathy and remaining 21 patients had other conditions such as urinary incontinence, secondary tumors and cystitis.

Standard medications and association between age and standard medications

Of the 116 patients with comorbidities, the mean number of medications prescribed each day was 4.6 medications (SD=2.8), with the minimum number of medications prescribed to a patient being one and the maximum being 14. There were 18 medication classes prescribed and the most frequently used were statins with 49/116 (42%) of patients being prescribed a statin as one of their standard medications. Furthermore, 48/116 (41%) were prescribed an antiplatelet agent, 40/116 (35%) were prescribed an α_1-antagonist and 37/116 (32%) of patients were prescribed a proton pump inhibitor as one of their standard medications. Additionally, 29/116 (25%) were prescribed an angiotensin II receptor antagonist, 28/116 (24%) were prescribed an ACE inhibitor and 25/116 (22%) of patients were prescribed an analgesic as one of their standard medications. Only six patients or 5% were prescribed the anticoagulant warfarin as one of their standard medications (Table 1). There was a significant association between the age and the number of standard medications prescribed, as demonstrated by Pearson correlation ($r = 0.281$, $p = 0.001$). There were 33 or 24% patients under the age of 65 and 102 patients or 76% aged 65 years and over. Furthermore, patients 65 years and over were more likely to suffer from comorbidities when compared to patients younger than 65 (Table 2).

Medications administered pre-operatively and peri-operatively

Of all patients, 7/135 (5%) were administered medications pre-operatively with all seven patients requiring the administration of paracetamol (acetaminophen). The mean number of medications administered peri-operatively was 4.24 medications (SD=1.9) with the minimum number of medications administered being one and the maximum number being 10. There were nine different medications that were administered to 10 or more patients during TURP. The most commonly administered medication was gentamycin with 116/135 (86%) of patients being

administered this drug during surgery. Propofol was administered to 92/135 (68%) and fentanyl was administered to 83/135 (61%) of patients during surgery. Additionally, paracetamol was administered to 46/135 (34%) whereas midazolam and metaraminol were administered to 36/135 (27%) of patients during surgery. Morphine was administered to 31/135 (23%), amoxicillin was administered to 23/135 (17%), rocuronium was administered to 11/135 (8%) and alfentanil was administered to 10/135 (7%) of patients during surgery.

Association between the number of standard medications prescribed, age, comorbidities and complications

Complications arising after TURP occurred in 48/135 (36%) of patients. The most common complications postoperatively from the second postoperative day until hospital discharge were haematuria, occurring in 41/48 (85%) and haematuria with clot retention, occurring in 24/48 (50%) of patients who suffered complications. Other complications included pain (8%), fever (6%) and infection (4%). Chi-square analyses showed a significant association between the number of standard medications prescribed and haematuria, χ^2 (12) = 21.50, p=0.04; and the number of standard medications prescribed and haematuria with clot retention χ^2 (12) = 24.97, p=0.015. In contrast, there was no significant association between the age and postoperative complications or between the types of medications used (antihypertensive, hypoglycaemic, lipid-lowering) and complications. However, it is important to note that 55% of patients taking oral hypoglycaemic agent metformin experienced haematuria and haematuria with clot retention after TURP (Table 1). Finally, calculation of Pearson correlation coefficient revealed a significant association between the age and comorbidities (r = 0.192, p = 0.025 which is expected as with aging co-morbidities become more prevalent.

Discussion

There are recent studies describing the relationship between anticoagulant and antiplatelet medications and the risk of complications associated with TURP (Kavanagh et al., 2011; Taylor et al., 2011). However, the relationship between other medication classes that are commonly administered to patients undergoing TURP and associated complications has not been investigated. This study investigated the different types of medications used and their relationship to complications arising from TURP. Various parameters within the patients' demographics were explored. Older surgical patients aged 65 and over are more susceptible to post-operative complications because they have higher morbidity rates than their younger counterparts and also as a result of physiological changes associated with aging process (Polanczyk et al., 2001; Turrentine, Wang, Simpson, & Jones, 2006). Post-operative complications such as haematuria, presence of blood clots in urine and infection can lead to longer length of hospital stay as well as increased number of medications prescribed to treat the complications. Due to the delicate physiology of older patients, these complications are associated with poor outcomes following hospitalization such as increased risk of falls, social and emotional withdrawal (Fried, Ferrucci, Darer, Williamson, & Anderson, 2004; Kristjansson et al., 2010; Saxton & Velanovich, 2011).

This study found that there was a significant association between the age and the number of standard medications prescribed as well as between the age and comorbid states of patients. As the probability of developing multiple comorbidities such as hypertension, type-2 diabetes mellitus, hypercholesterolemia, GORD, osteoarthritis and heart disease increases with age, older people are therefore likely to be prescribed multiple medications. Polypharmacy in older patients increases the possibility of 'prescribing cascades' where a cascade develops when an adverse drug event is misinterpreted as a new medical condition, thus requiring additional drug therapy and adding to the chances of complications due to drug-drug interactions occurring (Petrone &

Katz, 2005; Salazar, Poon, & Nair, 2007).

In this study, the mean age of patients undergoing TURP was 72 years of age. Therefore patients were more likely to be prescribed more medications, suggesting a greater potential for drug-drug interactions leading to complications. Additionally, age-dependent physiological changes such as reduction in muscle mass and total body water, increased body fat, and reduced serum albumin concentration will further increase the complexity and the management of drug interactions amongst older patients (Fulop, Worum, Csongor, Foris, & Leovey, 1985; Greenblatt, 1979). Thus, these age-dependent physiological changes will affect the pharmacokinetics and pharmacodynamics of medications and increase the likelihood of complications after TURP. With age, renal mass and a number of nephrons decrease which leads to a reduction in glomerular filtration rate and accumulation of drugs in the body (Mangoni & Jackson, 2004). Furthermore, the ageing process decreases drug metabolism by the liver which in turn increases the half-life of drugs potentiating their detrimental effects (Schmucker, 2001). The fact that the most common conditions in older patients are hypertension and chronic heart disease which further contribute to a reduction in hepatic and renal clearance (Klotz, 2009) it is not surprising that complications occur frequently after TURP.

Antiplatelets and anticoagulants increase the risk of postoperative bleeding thus they are withheld preoperatively (Taylor et al., 2011). However, there is an evidence to suggest that proton pump inhibitors and paracetamol increase the effects of anticoagulants, thus leading to an increased risk of haemorrhage and clot retention occurring during and/or after surgery (Blume, Donath, Warnke, & Schug, 2006). As GORD is common in older people, the likelihood of concomitant therapies is increased in this population. Combination of proton pump inhibitors and anticoagulants such as omeprazole and warfarin has been shown to decrease the clearance rate of the anticoagulant through omeprazole-induced competitive inhibition of CYP2C19 (Blume et al.,

2006). An inhibition of CYP2C19 is therefore associated with detrimental increase in the anticoagulant effect of warfarin (Teichert et al., 2011). Furthermore, paracetamol was shown to potentiate the anticoagulant effects of warfarin thus increasing the risk of bleeding. The potentiation of warfarin effect by paracetamol is likely to occur from inhibition of enzymes involved in vitamin K cycle (Pinson, Beall, & Kyle, 2013; Thijssen, Soute, Vervoort, & Claessens, 2004).

Another commonly used medication by older patients is metformin. Metformin is primarily excreted by the kidneys and its use is contraindicated in patients with renal impairment because of the risk of lactic acidosis (Connolly & Kesson, 1996). Our study showed that patients who had metformin ceased preoperatively did not suffer any complications post-operatively whereas 29% of patients who continued with metformin during surgery suffered haematuria and clot retention postoperatively. This novel information warrants further research into this class of hypoglycaemic medications. Additionally, further research should also extend to other medication classes including antidepressants especially selective serotonin reuptake inhibitors which are known to increase the risk of bleeding in healthy individuals and antihypertensives such as selective alpha-blockers which are found to be ceased in our study population.

The present study found a significant association between the number of standard medications prescribed and complications post TURP namely haematuria and haematuria with clot retention. A key explanation for these findings is that polypharmacy plays a role in increasing the chances of post-operative complications in patients on multiple standard medications. This theory is supported by the fact, that clot retention and haematuria occur despite cessation of medications that are well known to increase the risk of complications postoperatively. In this study, medications that were found to be commonly ceased before surgery included aspirin, prazosin, and tamsulosin. The presence of haematuria and haematuria with clot retention in patients who

had these medications ceased suggests that either these medications were not ceased for an adequate period pre-operatively, or that insufficient clearance of these medications led to drug interactions and thus post-operative complications. The ageing process is associated with pharmacokinetic and pharmacodynamic changes leading to increased sensitivity to several classes of medications in older patients. Due to these changes, the plasma concentration of anticoagulants and antiplatelets may have increased thus the cessation period was not sufficient for complete clearance. Alternatively, due to the insufficient clearance of these medications before surgery, interactions with other drugs that were prescribed may have further potentiated their therapeutic effects (Mangoni & Jackson, 2004).

Conclusion

This study provides novel information about the prescription and cessation of different classes of medications in older patients undergoing TURP. The number of standard medications prescribed to patients is directly associated with an increase in haematuria and haematuria with clot retention after TURP. Nurses who are the key-providers of hands-on care in these cases should implement detailed assessment of patients' medications and their physiological status in order to reduce these complications after TURP. The major limitation of this study was the small sample size. Even though the study was conducted in a large scale academic hospital over a 24-month period and included the whole population of patients undergoing TURP, the number of patients was still quite small.

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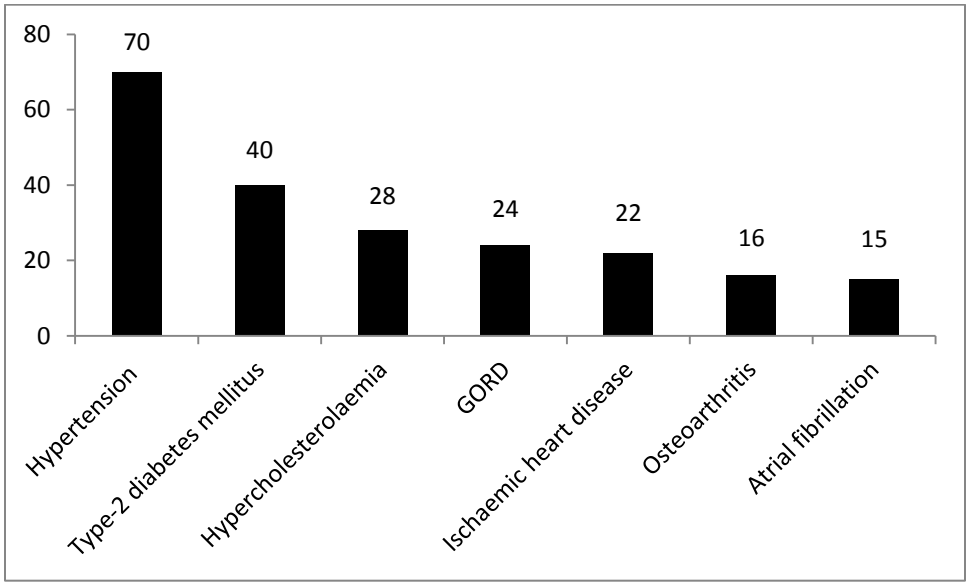
Figure 1 The most common comorbidities in patients undergoing transurethral resection of the prostate (n = 116, total number of patients with comorbidities). Data are shown separately for number of patients (n) with a hypertension, type-2 diabetes mellitus, hypercholesterolemia, GORD, ischemic heart disease, osteoarthritis and atrial fibrillation. Some patients had multiple overlapping comorbidities.

Figure


80
60
40
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15
Hypertension
Type-2 diabetes mellitus
Hypercholesterolaemia
GORD
Ischaemic heart disease
Osteoarthritis
Atrial fibrillation

Table 1 Standard medication classes prescribed to patients with comorbidities (n=116) and incidence of complications

Medication classes	Examples of medications	Number of patients on these medications	Number of patients with haematuria and haematuria/clot retention
Statins	Atorvastatin Simvastatin	49	1
Antiplatelets	Aspirin Clopidogrel	48	4
α_1-antagonists	Prazosin Tamsulosin	40	3
Proton pump inhibitors	Esomeprazole Pantoprazole	37	7
Angiotensin II antagonists	Candesartan Irbesartan	29	2
ACE inhibitors	Perindopril Ramipril	28	4
Analgesics	Paracetamol Tramadol	25	2
Ca^{++}-channel antagonists	Amlodipine Felodipine	24	0
β_2-agonists	Salbutamol Salmeterol	23	0
Biguanides	Metformin	22	12
β_1-antagonists	Bisoprolol Metoprolol	18	2
Sulfonylureas	Gliclazide Glimepiride	13	0
Steroids	Budesonide Fluticasone	11	0
Loop diuretics	Frusemide	10	0
Insulin	Lantus NovoRapid	9	2
5α-reductase inhibitors	Finasteride	8	0
Xanthine oxidase inhibitors	Allopurinol	7	1
Anticoagulants	Warfarin	6	2

Table 2 Presence of comorbidities within age groupings (less than 65 years of age and 65 years of age and over)

Age	Comorbidities	Comorbidities	Total number of patients
	Yes	No	
Less than 65 years	25 (75.8%)	8 (24.2%)	33
65 years and over	91 (89.2%)	11 (10.8%)	102