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Cardiac Failure Associated with Medical Therapy of Benign Prostatic Hyperplasia: A Population Based Study

Avril Lusty, D. Robert Siemens,* Mina Tohidi, Marlo Whitehead, Joan Tranmer and J. Curtis Nickel

From the Department of Urology (AL, DRS, JCN), Queen's University, Kingston, Ontario, Canada, Department of Oncology (DRS), Queen's University, Kingston, Ontario, Canada, Division of Cancer Care and Epidemiology (DRS), Queen's University Cancer Research Institute, Queen's University, Kingston, Ontario, Canada, Department of Surgery (MT), Queen's University, Kingston, Ontario, Canada, ICES-Queen's (MW, JT), Queen's University, Kingston, Ontario, Canada

Abbreviations and Acronyms

5ARI = 5-alpha reductase inhibitor

AB = α-blocker

ADG = Aggregated Diagnosis Group

BPH = benign prostatic hyperplasia

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* Correspondence: Department of Urology, 76 Stuart St., Queen's University, Kingston, Ontario K7L 2V7, Canada (telephone: 613-548-2411; email: robert.siemens@kingstonhsc.ca).

Purpose: Increased risk of cardiac failure with α-blockers in hypertension studies and 5-alpha reductase inhibitors in prostate studies have raised safety concerns for long term management of benign prostatic hyperplasia. The objective of this study was to determine if these medications are associated with an increased risk of cardiac failure in routine care.

Materials and Methods: This population based study used administrative databases including all men over 66 with a diagnosis of benign prostatic hyperplasia between 2005 and 2015. Men were categorized based on 5-alpha reductase inhibitor exposure and/or α-blocker exposure with a primary outcome of new cardiac failure utilizing competing risk models. Explanatory variables examined included exposure thresholds, formulations, age, and comorbidities associated with cardiac disease.

Results: The data set included 175,201 men with a benign prostatic hyperplasia diagnosis with 8,339, 55,383, and 41,491 exposed to 5-alpha reductase inhibitor, α-blocker and combination therapy, respectively. Men treated with 5-alpha reductase inhibitor and α-blocker, alone or in combination, had a statistically increased risk of being diagnosed with cardiac failure compared to no medication use. Cardiac failure risk was highest for α-blockers alone (HR 1.22; 95% CI 1.18−1.26), intermediate for combination α-blockers/5-alpha reductase inhibitors (HR 1.16; 95% CI 1.12−1.21) and lowest for 5-alpha reductase inhibitors alone (HR 1.09; 95% CI 1.02−1.17). Nonselective α-blocker had a higher risk of cardiac failure than selective α-blockers (HR 1.08; 95% CI 1.00−1.17).

Conclusions: In routine care, men with a benign prostatic hyperplasia diagnosis and exposed to both 5-alpha reductase inhibitor and α-blocker therapy had an increased association with cardiac failure, with the highest risk for men exposed to nonselective α-blockers.

Key Words: prostatic hyperplasia, heart failure, 5-alpha reductase inhibitors, adrenergic alpha-antagonists, lower urinary tract symptoms

BENIGN prostatic hyperplasia and cardiovascular diseases are common conditions in the aging male.[1,2] Mounting evidence suggests that a relationship between the two may be due to more than chance alone, potentially with shared pathophysiological processes.[3,4] Although still unclear, proposed underlying mechanisms of this association include cigarette smoking, high blood pressure, and dyslipidemia. Other suggested causal factors include oxidative stress, vascular calcification, and metabolic syndrome.[5] Chronic inflammation may also play a pivotal role in this link between BPH and cardiac

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diseases.[6] Finally, reports of increased risk of cardiovascular diseases secondary to α-blockers in hypertension studies and 5-alpha reductase inhibitors in prostate studies further complicate this association.[1,7]

5ARIs and ABs, either alone or as combination treatment, are the most common forms of management for men with lower urinary tract symptoms due to BPH.[8] Evidence from prospective randomized trials demonstrating an increased risk of cardiac failure with ABs for hypertension (alfuzosin in ALLHAT[7]) and 5ARIs as prostate cancer prevention (dutasteride in REDUCE[1]) have raised safety concerns among clinicians, as these medications are typically used as long-term management of BPH. Potential mechanisms for the associations between cardiac failure and 5ARIs include the deleterious impact on metabolic disorders and cardiac function through their anti-androgen effect and blockage of serum testosterone conversion to dihydrotesterone.[9] AB association with cardiac failure on the other hand may be linked to their vasodilatory effects and blood pressure variability.[10] However, results from subsequent nonrandomized studies linking 5ARIs and ABs with cardiac failure have been mixed.[11–15]

Importantly, difficulty controlling for confounding within studies of chronic conditions such as BPH is common and there is evidence that indicators of cardiovascular disease are more prevalent among patients starting drug treatment for BPH as compared to controls.[16] The objective of this population based study was to determine if medical management was associated with an increased risk of new cardiac failure in males with a BPH diagnosis in routine care. Secondarily, we aimed to determine the association of the primary outcome for those medically treated BPH patients with the duration of drug exposure (5ARIs and/or ABs) and whether there was an increased risk of cardiac failure based on AB selectivity.

METHODS

This was a population based retrospective cohort study using linked administrative databases to identify patients diagnosed with BPH in Ontario between January 1, 2005 and December 31, 2015. The maximum followup date was December 31, 2018. Ontarians over 65 years of age are eligible for the Ontario Drug Benefits program. As such, males aged 66 and over with a diagnosis of BPH with no recent past history of cardiac failure were included. Diagnoses were based on International Statistical Classification of Diseases and Related Health Problems (ICD) codes, both ICD-9 and ICD-10 versions, and included cardiac failure, congestive heart failure and ventricular failure. Exclusion criteria included absence of a valid Ontario health card, death at index, and those previously diagnosed with prostate cancer. The lookback window for the study excluded those with 5ARI use within 1 year of diagnosis, AB use within 1 year of diagnosis, and cardiac failure within 5 years of the index date of BPH diagnosis.

Linked administrative databases were used through the Institute for Clinical Evaluative Sciences. Each database is routinely used for research purposes and has been previously validated.[17] Linked records included those with the Discharge Abstract Database, Ontario Health Insurance Plan, physician claims database, Ontario Drug Benefits, and Same Day Surgery database. The quality and coding accuracy of these databases have been demonstrated in reabstraction studies.[18]

The primary outcome was a new diagnosis of cardiac failure after the index date of the BPH diagnosis. Subjects were categorized based on their exposure to typical medical therapy, including no treatment control, 5ARI monotherapy, AB monotherapy and 5ARI/AB combination therapy. Although there is no known additive or synergistic effect to develop cardiac failure with combination 5ARI and AB, these medications are frequently prescribed in combination, and as such combination treatment was included as a treatment group. Other covariates included age and comorbidities associated with cardiac disease, including a history of atherosclerosis, hypertension, diabetes, chronic ischemic heart disease and a history of myocardial infarction in the 5 years preceding the index diagnosis. An overall score for comorbidities, using the Johns Hopkins Aggregated Diagnosis Groups, was utilized. The different formulations of BPH medical therapy were categorized as a 5ARI (including both finasteride and dutasteride) or AB (including selective and nonselective). Further subcategorization of AB into selective (silodosin and tamsulosin) and nonselective (including terazosin, doxazosin and alfuzosin) was performed. Exposure time to 5ARIs and/or ABs was collected and listed as number of days of medication use. Continuous drug use was calculated as a rate of ratio of days of >0.82 ($\sim$300/365 days). Cumulative incidence function estimate was also determined based on drug exposure.

A Cox proportional hazards regression model was used for statistical analysis. Descriptive statistics were used for baseline characteristics describing the cohorts based on medication use. Univariate and multivariable competing risk analyses were performed to assess the risk of cardiac failure associated with utilization of medical therapy compared to those with no medication use starting at the index BPH diagnosis date. Given evidence of differential baseline cardiovascular risk between those exposed and nonexposed to medical therapy, subsequent analysis only included those exposed to BPH drugs and risk of cardiac failure was measured from the start of first drug exposure. The data were also interrogated to determine any association of risk of cardiac failure and duration of drug exposure. Drug exposure was analyzed as a continuous variable as well as categorization into tertiles due to concerns about linearity but also to determine any threshold effects given the common early discontinuation of these drugs for side effects and lack of desired efficacy. Further analysis was performed to determine if there was an increased risk of cardiac failure with the use of nonselective ABs compared to selective ABs. Note that the events utilized in the competing risk models were subdistributional hazards. For all statistical methods a 2-sided p value of <0.05 was considered statistically significant. Data were analyzed using SAS Stat 14.3.

RESULTS

After exclusions, 175,201 men diagnosed with BPH met study criteria, with 69,988, 8,339, 55,383 and 41,491 subjects in the no medication control, 5ARI alone, AB alone and combination treatment group, respectively. The median age of the cohort was 73 years (69–78) (table 1). The baseline characteristics between men in each of the 4 groups were similar, including the listed cardiovascular risk factors (table 1). The exposed and nonexposed cohorts demonstrate moderately comorbid groups, including a history of myocardial infarction, hypertension, chronic obstructive pulmonary disease and diabetes.

The total number of days on drug and measures of continuous use, defined by a rate of ratio of drug exposure >0.82, demonstrate that those on AB monotherapy had a median number of 450 days of exposure (92–1,407), which is similar to the other exposure groups (table 1).

In comparison to those with a BPH diagnosis and no exposure to medical therapy, men prescribed ABs alone, combination therapy or 5ARIs alone had an increased risk of cardiac failure with HR of 1.22

Table 1. *Baseline characteristics of men diagnosed with BPH in Ontario between 2005 and 2015 according to BPH drug exposure*

	No Medications		5-ARI		α-Blocker		5-ARI + α-Blocker	
No. pts	69,988		8,339		55,383		41,491	
Yrs age:								
Mean±SD	74.05±6.58		74.31±6.30		74.26±6.38		74.11±6.17	
Median (IQR)	73	(69–78)	73	(69–78)	73	(69–78)	73	(69–78)
No. yrs age (%):								
66–70	26,563	(38)	2,865	(34)	19,219	(35)	14,348	(35)
71–75	18,191	(26)	2,310	(28)	15,493	(28)	11,825	(29)
76–80	12,745	(18)	1,697	(20)	10,866	(20)	8,562	(21)
81+	12,489	(18)	1,467	(18)	9,805	(18)	6,756	(16)
No. myocardial infarction (%)	2,426	(3)	248	(3)	2,117	(4)	1,317	(3)
No. congestive heart failure (%)	257	(0)	32	(0)	220	(0)	116	(0)
No. peripheral vascular disease (%)	1,359	(2)	143	(2)	996	(2)	656	(2)
No. cerebrovascular disease (%)	1,933	(3)	217	(3)	1,690	(3)	1,099	(3)
No. chronic obstructive pulmonary disease (%)	2,013	(3)	205	(2)	1,734	(3)	1,074	(3)
No. diabetes without complications (%)	3,401	(5)	371	(4)	2,940	(5)	1,943	(5)
No. diabetes with complications (%)	2,553	(4)	224	(3)	2,460	(4)	1,466	(4)
No. primary cancer (%)	3,344	(5)	288	(3)	2,108	(4)	1,179	(3)
Aggregate Diagnosis Group:								
Mean±SD	10.82±4.24		10.66±4.19		11.27±4.20		11.02±4.25	
Median (IQR)	11	(8–14)	11	(8–14)	11	(8–14)	11	(8–14)
No. Aggregate Diagnosis Group (%)								
0–6	11,376	(16)	1,401	(17)	7,417	(13)	6,120	(15)
7–9	15,462	(22)	1,885	(23)	11,137	(20)	8,524	(21)
10–11	12,494	(18)	1,515	(18)	9,906	(18)	7,473	(18)
12–13	11,741	(17)	1,390	(17)	9,980	(18)	7,341	(18)
14+	18,915	(27)	2,148	(26)	16,943	(31)	12,033	(29)
No. Major Aggregate Diagnosis Groups (%):								
0	10,494	(15)	1,319	(16)	7,345	(13)	5,969	(14)
1	17,271	(25)	2,183	(26)	12,905	(23)	10,325	(25)
2	16,626	(24)	2,025	(24)	13,709	(25)	10,451	(25)
3	12,236	(17)	1,409	(17)	10,358	(19)	7,548	(18)
4 +	13,361	(19)	1,403	(17)	11,066	(20)	7,198	(17)
No. days 5-ARI exposure:								
Mean±SD			1,315.22±1,206.32				1,170±1,131	
Median (IQR)			960	(240–2,196)			780	(220–1,860)
No. days α-blocker exposure:								
Mean±SD					909±1,067		1,385±1,241	
Median (IQR)					450	(92–1,407)	1,050	(320–2,160)
No. days exposure to concurrent use of 5-ARI + α-blocker:								
Mean±SD							1,148.77±1,173.17	
Median (IQR)							727	(163–1,854)
No. days α-blocker exposure (%)	0	(0)	0	(0)	55,383	(100)	41,491	(100)
No. days 5-ARI exposure (%)	0	(0)	8,339	(100)	0	(0)	41,491	(100)
Days with 5-ARI/days on study:								
Mean±SD			0.89±0.18				0.87±0.22	
Median (IQR)			1	(1–1)			1	(1–1)
Days with α-blocker/days on study:								
Mean±SD					0.83±0.27		0.80±0.27	
Median (IQR)					1	(1–1)	1	(1–1)
No. 5-ARI compliance (%)	0	(0)	5,827	(70)	0	(0)	28,228	(68)
No. α-blocker compliance (%)	0	(0)	0	(0)	29,745	(54)	29,999	(72)

Percentages presented are column percentages.

Table 2. *Subdistributional hazard ratios for new cardiac failure diagnosis*

	Adjusted Model		
	Rate	Hazards Ratio (95% CI)	p Value
Exposure group:			
5-ARI exposure	11.01	1.09 (1.02–1.17)	< 0.001
α-Blocker	12.08	1.22 (1.18–1.26)	
Both 5-ARI + α-blocker	11.92	1.16 (1.12–1.21)	
No medications	9.41	Reference	
Yrs age at index date:			
66–70	5.69	Reference	< 0.001
71–75	9.65	1.58 (1.51–1.65)	
76–80	14.33	2.25 (2.15–2.35)	
81+	19.96	3.26 (3.12–3.40)	
History of dyslipidemia:			
No	10.21	Reference	< 0.001
Yes	18.39	1.16 (1.11–1.22)	
History of atherosclerosis:			
No	10.73	Reference	< 0.001
Yes	29.70	1.70 (1.55–1.87)	.
History of hypertension:			
No	6.72	Reference	< 0.001
Yes	13.03	1.51 (1.46–1.57)	.
History of diabetes:			
No	9.46	Reference	< 0.001
Yes	15.05	1.47 (1.42–1.51)	.
History of chronic ischemic heart disease:			
No	9.30	Reference	< 0.001
Yes	22.83	1.93 (1.86–2.01)	.
History of myocardial infarction in 5 yrs preceding index:			
No	10.76	Reference	0.51
Yes	19.15	1.03 (0.95–1.12)	.

Adjusted for all covariates shown in Cox Proportional Hazards Model. Time start from BPH diagnosis.

(95% CI 1.18–1.26), 1.16 (95% CI 1.12–1.21) and 1.09 (95% CI 1.02–1.17), respectively (table 2). In a multivariable competing risk analysis, men treated with 5ARIs alone appeared to have less cardiac failure than those prescribed ABs, either as ABs alone or as combination therapy, p value = 0.02 with HR of 1.10 (95% CI 1.02–1.18) for ABs and 1.05 (95% CI 0.98–1.14) for combination treatment (table 3). In this analysis, men treated with ABs alone had a higher risk of cardiac failure than those exposed to combination therapy (table 3). There was an increased risk of cardiac failure in subjects treated with nonselective ABs blockers (5,631) compared to selective ABs (43,490) with a HR of 1.08 (95% CI 1.00–1.17), p value = 0.04 (table 3). All analyses controlled for age and specified cardiac history variables. The cumulative incidence function estimate further demonstrates the increased risk of cardiac failure with AB exposure having the highest cumulative incidence (see figure). There was no significant of effect of time on ABs and a new cardiac failure diagnosis when analyzed as a continuous variable. Because of concern for the assumption of linearity and a desire to determine if there was any threshold of drug exposure on

Table 3. *Subdistributional hazard ratios for new cardiac failure diagnosis in men initiating medical therapy*

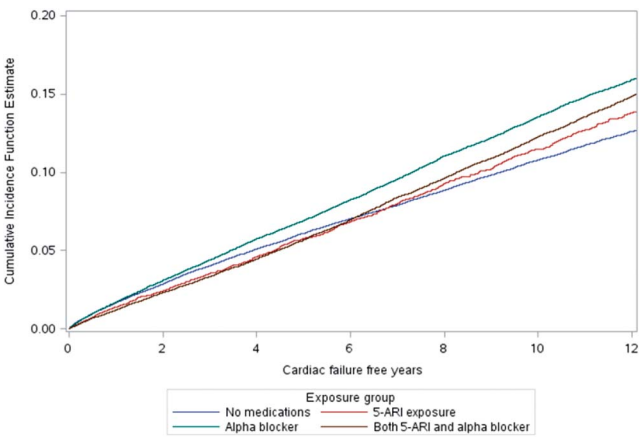
		Adjusted Model	
Drug Exposure	Rate	Hazard Ratio (95% CI)	p Value
5-ARI exposure	9.81	Reference	0.02
α-Blocker	10.59	1.10 (1.02–1.18)	
Both 5-ARI + α-blocker	11.27	1.05 (1.00–1.14)	
Nonselective α-blocker	12.15	1.08 (1.00–1.117)	0.04
Selective α-blocker	9.81	Reference	

Adjusted for age, dyslipidemia, atherosclerosis, hypertension, diabetes, chronic ischemic heart disease, myocardial infarction in Cox Proportional Hazards Model. Time starts from first drug exposure.

outcome, we also analyzed drug exposure based on tertiles (lowest tertile less than 420 days). Tertile analysis demonstrated that longer drug exposure was significantly associated with an increased risk of cardiac failure for those exposed to AB monotherapy (HR 1.16, 95% CI 1.09–1.24), and in selective ABs (HR 1.14, 95% CI 1.05–1.23).

DISCUSSION

This study aimed to determine if the most commonly prescribed medications for BPH, 5ARIs and ABs either alone or in combination, were associated with an increased risk of cardiac failure in routine care. Utilizing this large population database, including men with a BPH diagnosis and no previous history of cardiac failure, we found that exposure to 5ARIs and/or ABs had a higher rate of new cardiac failure diagnosis compared to those unexposed to these medications, or the control group. We found that the cumulative incidence of cardiac failure was higher in those exposed to ABs, prescribed either alone or in combination with 5ARIs, compared to 5ARIs alone. These initial results guided subsequent analysis of the cohort to further interrogate the association of cardiac failure with ABs, which



Cumulative incidence function curve of new cardiac failure by exposure group.

remained significant after controlling for key cardiovascular covariates. Furthermore, nonselective AB exposure was associated with a higher risk of cardiac failure than selective ABs with a duration dependent effect to drug exposure when analyzed as a threshold greater than 420 days.

Cardiac failure in the aging male population is prevalent, as is a concurrent diagnosis of BPH and its treatment with 5ARIs and/or ABs.[19] From the entire cohort, 69,988 men, (39.9%) over 65 years old diagnosed with BPH had no indication of medical treatment. It is possible that this cohort of men with either less significant symptoms, misclassification or different expectations for symptomatic control could have varying baseline cardiac risk factors. Subsequent analyses of the primary outcome in this study focused only on those exposed to BPH drugs. The majority of men in this cohort were treated with typical BPH medical therapy and therefore a significant number of patients potentially at risk to longer-term consequences of 5ARIs and ABs, specifically the development of new cardiac failure.

It follows that selective ABs, which target alpha-1-A receptors in the bladder neck and prostate, have decreased systemic effects on the alpha-1-B and alpha-1-D receptors found in the arterial smooth muscle and bladder smooth muscle and spinal cord, respectively.[10] The current results show the downstream effects this exposure difference can have on patient's cardiac health. Nonselective ABs had a higher incidence of new cardiac failure diagnosis than those exposed to selective ABs, which should be acknowledged, and, although not practice changing, continued efforts made for organ-specific treatment to be used in clinical practice. We found a small but significant duration effect size for AB monotherapy, with a HR of 1.16 (CI 1.08−1.24) for AB monotherapy, even after controlling for robust risk factors including hypertension, diabetes and previous myocardial infarction. There are limited data describing the average duration of BPH medical management; however, studies have suggested that men continue these medications for several years, with primary care physicians prescribing a longer course of treatment than urologists, as well as large cohort trials following patients treated with BPH medications for up to 4 years.[1,20−23] It is important that urologists and primary care physicians be aware of this potential link.

The results from this study echo those of the ALLHAT trial[7] and REDUCE,[1] and provide additional incremental knowledge with respect to ABs and 5ARIs, respectively. These 2 landmark trials have described associations between BPH medications and cardiac failure. REDUCE, a 4-year, randomized, placebo-controlled study of 6,729 men, aimed to determine if dutasteride reduced the risk of prostate cancer among men at increased risk for the disease.[1] They found a higher incidence of cardiac failure in men prescribed 5ARIs for prostate cancer prevention (0.7%; 30 patients) compared to placebo (0.4%; 16, $p=0.03$).[1] A significant number of REDUCE subjects also had concurrent BPH related lower urinary tract symptoms.[24] Some have suggested the increased risk of cardiac failure with 5ARIs stems from its mechanism of action, decreasing the serum conversion of testosterone to dihydrotestosterone, resulting in deleterious effects on the cardiovascular system;[9] however, there is still no consensus. ALLHAT aimed to determine if treatment with a calcium channel blocker or an angiotensin-converting enzyme inhibitor lowered the incidence of coronary heart disease or cardiovascular disease events versus treatment with a diuretic.[7] The initial trial design included doxazosin; however, this study treatment group was stopped secondary to increased cardiac events.[25] This landmark trial was among the first to emphasize a potential link between ABs and cardiac failure, particularly in hypertensive patients.[10,25] Proposed mechanisms of this association include less optimal blood pressure control in hypertensive patients and greater blood pressure lability detrimental to patients with higher risk cardiac disease.[7,25] In this current retrospective cohort of all patients diagnosed with BPH, patients had varying past history of cardiac diseases and risk factors, with 66%−69% having documented hypertension. Nonetheless, after controlling for these important explanatory variables we still demonstrate some association with AB, specifically with nonselective ABs, and risk of cardiac failure.

Although ALLHAT and REDUCE provided prospective evidence for the association between these medications and cardiac failure, they have limitations which restrict the ability to make firm conclusions about 5ARI and AB association with cardiac failure. The primary objective of REDUCE was not designed to assess the association with cardiac failure and did not control for men diagnosed with BPH and not on active BPH treatment.[1] ALLHAT did not include information regarding BPH diagnosis, as it was not designed to specifically address the BPH population.[7] Those studies designed specifically to assess the association between BPH, its pharmaceutical treatment and cardiac failure have not consistently included a control group and/or have lacked information regarding AB use, which is paramount to include when making conclusions in this disease space.[11−15,26]

This study takes into account these previous research limitations with the inclusion of a control group in our analysis as well as assessing the effect of ABs in detail, AB formulation, selectivity and time exposed to drug. The data also include a large provincial database, which ensures the capture of provincial prescribing habits. Limitations of this

study include those of all similar population based investigations, including its retrospective nature and the accuracy of available diagnostic administrative codes. Another limitation in interpreting these results is that Ontario, though relatively diverse with approximately 20% self-identified as nonWhite, will be quite different in ethnic background than seen in other jurisdictions. Furthermore, it is not possible to infer the compliance of BPH medication use as compared to drugs dispensed; however, the measures of continuous prescription renewal in this study would suggest relatively close adherence.

CONCLUSION

This large, long-term, retrospective analysis of men with BPH found a statistically significant increase in new cardiac failure in men exposed to both 5ARI and AB therapy with the highest risk for men exposed to AB (alone or in combination with 5ARI). When isolated for AB selectivity, the results found a higher risk of cardiac failure associated with nonselective ABs than selective ABs as well as a duration dependent effect of AB exposure, with longer drug exposure associated with increased risk of cardiac failure.

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EDITORIAL COMMENTS

Siemens et al present a well-designed study analyzing the risk of cardiac failure in patients on α-blocker therapy. This retrospective, population based study includes patients with a diagnosis of BPH on 5-alpha reductase inhibitors, AB monotherapy, combination 5ARI and AB treatment, and no treatment. The authors have analyzed the effect of selective AB versus nonselective AB on cardiac failure incidence as well. As expected, nonselective ABs are associated with an increased risk of cardiac failure, when compared to selective ABs, combination treatment and 5ARIs alone. This study should alert health care providers to curtail the prescription of this class of drugs for patients with BPH. The duration of treatment was found to be a risk factor for cardiac failure even in patients receiving selective ABs (HR 1.14, 95% CI 1.05−1.23). What follows is the proposition that urologists should offer earlier surgical intervention in patients who, although comfortable on ABs, have taken the medication for a longer duration. What is the safe duration for selective AB prescription? And what are the risk factors for cardiac failure amongst this population? Further, the study only included patients over the age of 65. What about the incidence of cardiac failure in patients under 65 years of age who need treatment for BPH? The study was done on a multi-ethnic population (22% nonWhite). What is the influence of ethnicity on cardiac failure risk? More studies on these subjects are needed.

Omar Salim Akhtar
Government Medical College
Srinagar, Kashmir, India

It has become established that the first line therapy for male lower urinary tract symptoms is medical therapy.[1] This has been the mainstay for over 20 years with the arrival of the first long-acting α-blocker. Over time, many medical side effects have been found to be associated with medical therapy for male lower urinary tract symptoms including decreased libido, erectile and ejaculatory dysfunction, fatigue and possible psychological adverse events.[2]

This current population based retrospective cohort study adds to the mounting and concerning side effects associated with medical therapy for male lower urinary tract symptoms. Using a large population data set with over 175,000 men, including men with BPH and no previous history of cardiac failure, Siemens et al demonstrate a significant increase in new cardiac failure diagnosis with the use of α-blockers (nonselective > selective) and 5ARIs (combo AB > 5ARI mono). Due to already significant side effects associated with 5ARIs, most patients were given AB as monotherapy. Unfortunately, this was the population most associated with new onset cardiac failure.

This could be the final nail in the medical therapy for male lower urinary tract symptoms coffin. With so many side effects already associated with 5ARIs and ABs and with so much surgical innovation, might this finally be the time for early surgical treatment? Surgical innovation has evolved over the past 10 years, with surgical options for every prostate based on the patient's specific values, perspectives and objectives.[3] Without even mentioning the detrimental bladder effects of delayed surgical management, it may be time to start advocating for early surgical therapy for our patients. At the very least, a more fulsome informed consent conversation needs to take place when prescribing medical therapy for male lower urinary tract symptoms, especially in patients with cardiac disease. Finally, a greater awareness amongst prescribing primary care physicians and specialists needs to be advocated.

Naeem Bhojani and Kevin C. Zorn
Division of Urology, Centre Hospitalier de l'Université de Montréal
University of Montreal
Ontario, Canada

Dean Elterman
Division of Urology, University Health Network
University of Toronto
Ontario, Canada

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REPLY BY AUTHORS

We read with interest the proffered editorials on our real-world study describing an association of medical therapy for BPH/male lower urinary tract symptoms and new congestive heart failure. We agree that the results add to the evolving narrative of longer-term consequences of medical management, which is often overseen by our primary care colleagues. How we respond to such findings as a specialty community is crucial. Although large observational data sets representing routine clinical care can lead to insight in the effectiveness and quality of our care (as well as identify less common adverse events), its inherent limitations impede endorsement for substantive change in evidence-balanced, patient centered decision making. Nonetheless, we very much agree with the editorials that these results, hopefully confirmed and expanded by future investigations, should add to enhanced awareness and allow better conversations with our patients about choices for contemporary BPH/male lower urinary tract symptoms management.