Supplementary Online Content

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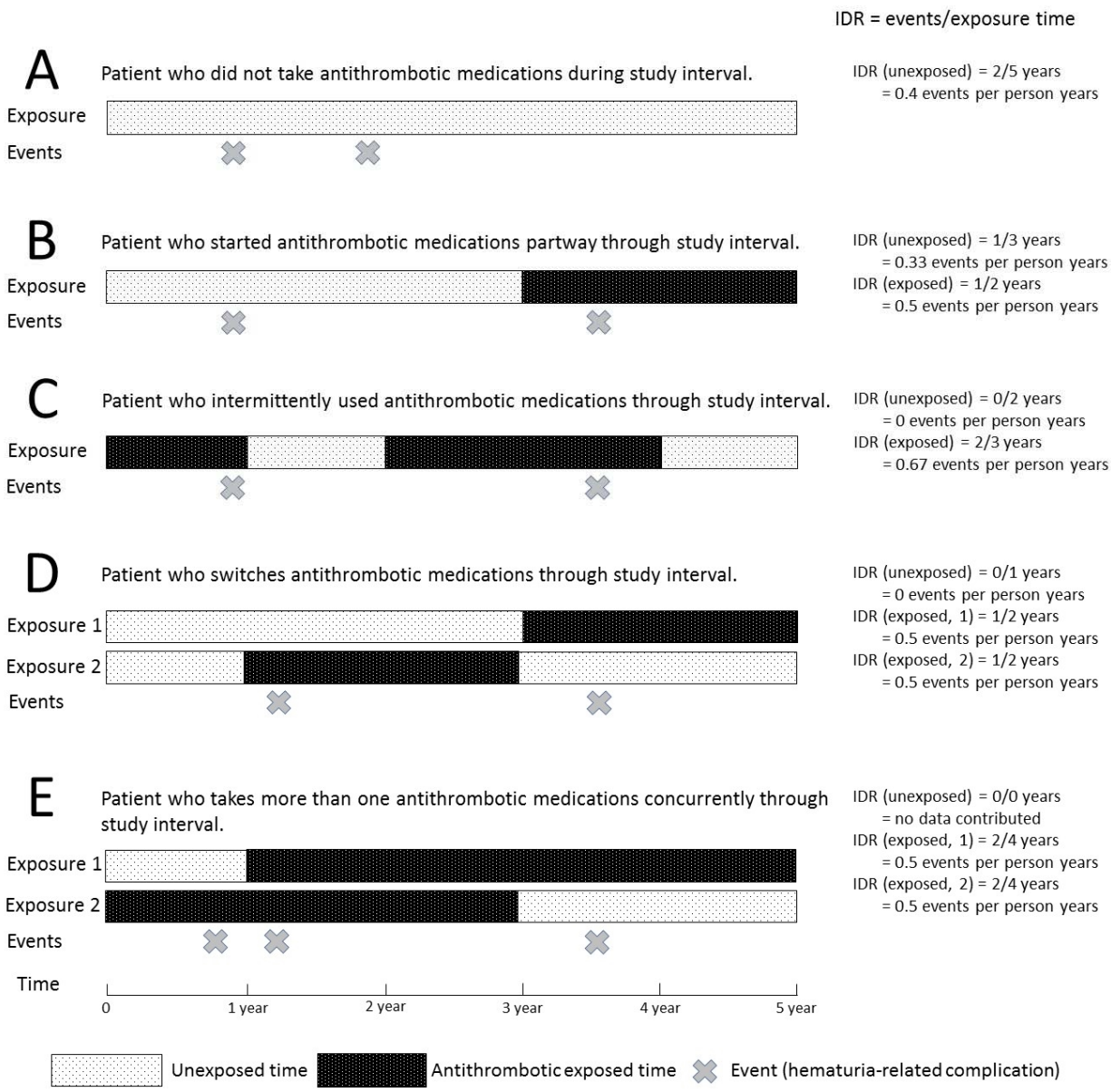
This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure. Schematic of Time-Varying Intermittent Exposure to Antithrombotic Medications, Illustrating the Calculation of Incidence Density Rates. Stippled area refers to time during which the patient in question was not exposed to an antithrombotic medication. The dark shaded area refers to time during which the patient was actively exposed to antithrombotic medications based on an active prescription. The "x" refer to hematuria-related events. Events are attributed to the exposure status (exposed or unexposed) immediately above the "x". The column on the right refers to the calculation of incidence density rates (IDR).

(A) Example of a patient who was never exposed to antithrombotic medications during the study interval. (B) Example of a patient who began an antithrombotic medication partway through the study interval. (C) Example of a patient who used antithrombotic medications intermittently throughout the study interval. (D) Example of a patient who switched antithrombotic medications during the study interval. (E) Example of a patient taking more than one antithrombotic medication concurrently.



Note: IDR = incidence density rate.

eTable 1. Medications Included in Exposure Definition	
Medication	Drug Identification Numbers
ANTI-PLATELET AGENTS	
Acetylsalicylic acid (ASA) >82 mg	02234510, 00180041, 01922246, 02245443, 02252856, 02303299, 02238645, 02252864, 00718831, 02246103, 00095494, 02152746, 02245367, 02332450, 02332469, 00472468, 00530336, 02270323, 02387492, 00785547, 00582867, 02247550, 02352427, 02352435, 02150425, 02150417, 02150336, 02150328, 02316897, 02316889, 02238670, 02264706, 02264722, 02292726, 00510696, 02010526, 00472476, 00794244, 02050161, 00010332, 01905392, 00852015, 00010340, 00419508, 02245729, 02252228, 02426625, 00226327, 00176206, 00176192, 00800511, 02242978, 01966375, 01966367, 01941895, 02252201, 02243051, 02237579, 02239741, 02251906, 02351544, 00216666, 00229296, 00040851, 02284529, 02284537, 02285371, 02229736, 00608157, 00608211, 00608238, 00608181, 00608203, 02245887, 01934791, 01934783, 02230949, 01971417, 02242406, 01971387, 01971409
Dipyridamole	02242119, 00895644, 00895652, 00895660, 00571237, 00571245, 00601845
Clopidogrel	02303027, 02252767, 02398591, 02416387, 02385813, 02394820, 02400553, 02378507, 02415550, 02422255, 02408910, 02351536, 02238682, 02330555, 02348004, 02379813, 02379819, 02359316 02293161, 02388065
Prasugrel	02349124
Ticagrelor	02368544, 02455005
Ticlopidine	02237701, 02243808, 02239744, 02243327, 02236848
ORAL ANTICOAGULANTS	
Warfarin	02242924, 02242925, 02242926, 02242927, 02242928, 02242929, 02245618, 01918362, 01918311, 01918346, 01918338, 02240205, 02007959, 01918354, 02240206, 02244462, 02244463, 02244464, 02244465, 02244466, 02244467, 02287498, 02287501, 02287528, 02242680, 02242681, 02242682, 02242683, 02242684, 02242685, 02242686, 02242687, 02242697
Rivaroxaban	02316986, 02378604, 02378612, 02441535
Dabigatran	02312433, 02312441, 02358808
Apixaban	02377233, 02397714

eTable 2. Outcome Definitions			
	ICD-10 diagnostic code	OHIP billing code	Canadian Classification of Health Interventions procedural code
Gross hematuria	R31.0		
Cystoscopy		Z606, Z607	2.PM.70.BA
Clot removal/irrigation		Z608, E783	1.PM.54.CA-TS
Control of bladder bleeding			1.PM.13.BA-Z9, BA-C2
Catheterization		Z611	1.PM.52.BA-TS, CA-TS

eTable 3. Validation of Administrative Data Sources		
Data source	Accuracy	Validation study
Ontario Drug Benefit	0.7% error rate	Levy et al. *Can J Clin Pharmacol*. 2003;10(2):67.
CIHI Discharge Abstract Database	Agreement with chart abstraction: -demographics: 95-100% -diagnoses: 1. median kappa 0.81 (IQR 0.70-0.87) 2. median sensitivity 0.82 (IQR 0.71-0.89) 3. median PPV 0.82 (IQR 0.84-0.89)	Juurlink et al. *Canadian Institute for Health Information Discharge Abstract Database: A validation study.* Toronto, Ontario, Canada: Institute for Clinical Evaluation Sciences; 2006
OHIP database	Data completeness 99% Agreement with chart abstraction: -primary diagnosis: 81-96% -procedures: 88-96%	Williams and Young. A summary of studies on the quality of health care administrative databases in Canada. In: Goel V, Williams J, Anderson G, al. E, eds. *Patterns of Health Care in Ontario, Canada: The ICES Practice Atlas*. Ottawa, Ontario, Canada: Canadian Medical Association; 1996:339.
Ontario Cancer Registry	Greater than 95% complete	Robles et al. *J Clin Epi*. 1988;41(5):495.

eTable 4. Medications Included in BPH Medication Exposure	
Medication	Drug Identification Numbers
ALPHA-BLOCKERS	
Silodosin	2361663, 2361671
Tamsulosin	2238123, 2270102, 2281392, 2294265, 2294885, 2295121, 2298570, 2319217, 2331780, 2340208, 2352419, 2362406, 2366231, 2368242, 2413612, 2427117, 2429667
Alfuzosin	2245565, 2304678, 2314282, 2315866, 2414759, 2443201, 2447576
Terazosin	2396289, 2350475, 2246544, 2218941, 2237476, 2243518, 2234502, 2233047, 2230805, 2350483, 2396297, 2230806, 818682, 2230806, 2233048, 2234503, 2243519, 2243747, 2237477, 2218968, 2218976, 2237478, 2243520, 2234504, 2233049, 2230807, 818666, 2396300, 2350491, 2218984, 2230808, 2233050, 2234505, 2243521, 2243749, 2218984, 2350505, 2396319, 818674
Doxazosin	2240498, 2240588, 2242728, 2243215, 2244527, 2240978, 2246332, 1958100, 2246333, 2240979, 2244528, 2243216, 2242729, 2240589, 2240499, 1958097, 2240500, 1958119, 2240590, 2242730, 2243217, 2244529, 2240980, 2246334
5-ALPHA REDUCATASE INHIBITORS	
Finasteride	2428741, 2445077, 2447541, 2447568, 2405814, 2348888, 2322579, 2306905, 2348500, 2356058, 2355043, 2354462, 2357224, 2350270, 2365383, 2371820, 2389878, 2010909
Dutasteride	2404206, 2408287, 2393220, 2412691, 2424444, 2428873, 2416298, 2421712, 2443058, 2427753, 2434369, 2247813

eTable 5. Sensitivity Analysis: Multivariable Negative Binomial Regression Models Assessing the Association Between Exposure to Antithrombotic Agents (Primary Exposure) and Hematuria-Related Complications, Using a limited definition of Urologic Procedures (Study Interval Between 2002-2014). Incidence density rates expressed as the number of events per 1000 person-years. Rate ratios comparing antithrombotic exposed and unexposed periods, with stratification by patient age due to a significant interaction between these two variables.

	Effect of antithrombotic medication exposure, stratified by age at prescription									
	Patients 66-69 years		Patients 70-74 years		Patients 75-79 years		Patients 80-84 years		Patients ≥85 years	
	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed
Sample size	1,254,546	388,435	180,692	158,444	127,262	130,623	77,235	80,197	69,432	51,194
Exposure time (person-years)	9,166,367	563,189	2,966,576	605,332	2,008,765	607,366	1,082,624	473,134	640,373	351,500
Any hematuria-related complication										
Number of events	593,897	53,291	241,846	68,316	163,409	73,767	82,443	54,698	38,804	32,343
Incidence density rate	64.791	94.624	81.524	112.857	81.348	121.454	76.151	115.608	60.596	92.014
Adjusted rate ratio (95% CI, p-value)*	1.19 (1.17-1.22, <0.001)		1.56 (1.53-1.59, <0.001)		1.77 (1.73-1.81, <0.001)		1.80 (1.75-1.83, <0.001)		1.57 (1.53-1.62, <0.001)	
Urologic procedures										
Number of events	530,257	44,664	216,259	57,751	144,709	61,969	71,419	45,272	31,968	25,532
Incidence density rate	57.848	79.306	72.899	95.404	72.039	102.029	65.968	95.685	49.921	72.637
Adjusted rate ratio (95% CI, p-value)*	1.11 (1.09-1.14, <0.001)		1.47 (1.44-1.50, <0.001)		1.65 (1.61-1.68, <0.001)		1.64 (1.60-1.68, <0.001)		1.36 (1.32-1.40, <0.001)	

*models adjusted for effect of participant gender, comorbidity, rurality, income quintile and geographic region of residence.

eTable 6. Standardized Incidence Ratios (SIR) of Potential Outcomes of Hematuria-Related Investigations (Study Interval Between 2002-2014)

Diagnosis	Men and women		Total sample size	Total person-years	Men		Total sample size	Total person-years	Women		Total sample size	Total person-years
	Number	SIR (95% CI)			Number	SIR (95% CI)			Number	SIR (95% CI)		
Bladder cancer	5646	2.38 (2.32 - 2.44)	21,495,463	2,600,519.0	4409	2.33 (2.26 - 2.40)	9,353,443	1,245,757.9	1237	2.17 (2.06 - 2.30)	12,142,120	1,354,762.0
Kidney cancer	774	0.64 (0.59 - 0.68)	21,495,463	2,600,519.0	502	0.64 (0.59 - 0.70)	9,353,443	1,245,757.9	272	0.59 (0.52 - 0.66)	12,142,120	1,354,762.0
Prostate cancer	n/a	n/a			6683	0.75 (0.73 - 0.77)	9,353,443	1,245,757.9	n/a	n/a		
Benign prostatic hypertrophy	n/a	n/a			61,081	2.45 (2.43 - 2.47)	9,353,443	1,245,757.9	n/a	n/a		
BPH-therapy with 5-ARI	n/a	n/a			26,983	1.33 (1.31 - 1.35)	9,353,443	1,245,757.9	n/a	n/a		
Note: BPH – benign prostatic hypertrophy; n/a – not applicable.												

eTable 7. Continuous Length of Time That Patients Spend on Each Drug

Drug type	Median time on drug (days) (Interquartile Range)
Any anticoagulant	114 (44-317)
ASA	114 (104-293)
Apixaban	97 (44-194)
Dabigatran	133 (44-325)
Other anti-platelets	199 (104-390)
Rivaroxaban	44 (28-171)
Warfarin	74 (44-152)