

Supplemental Online Content

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

eMethods 1. Details about Danish nationwide registries

Healthcare utilization data was abstracted from 3 Danish nationwide registries: the National Prescription Registry, the National Patient Register, and the Civil Registration System. Virtually all medical care in Denmark is furnished by the national health authorities, allowing population-based register linkage studies covering all legal residents of Denmark. Data was used from 1997 to 2016.

The Danish National Prescription Registry contains data, including date, dose and days supplied, for all prescription drugs dispensed at community pharmacies (e.g., it does not include inpatient medication usage) for Danish citizens since 1995. The medications are categorized according to the Anatomic Therapeutic Chemical (ATC) index, a hierarchical classification system developed by the WHO.

The National Patient Register contains nationwide data on all non-psychiatric hospital admissions from 1997 as well as all psychiatric inpatient, both non- and psychiatric outpatient, and emergency room contacts since 1995. Diagnoses were encoded in ICD-10 from 1994 to present.

The Civil Registration System contains data on date of death and migration to and from Denmark, allowing us to track all of the subjects.

Data was linked between the databases using the personal identification number, a unique identifier assigned to all Danish residents since 1968.

eMethods 2. Drug identification codes

Danish Registry

The Danish cohort has medication information encoded using the ATC.

The study drugs were terazosin (G04CA03), doxazosin (C02VA04), alfuzosin (G04CA01, G04CA51), and tamsulosin (G04CA02 and G04CA52-53). Other alpha blockers were those under ATC codes C02C* and G04CA* that were not one of the study drugs.

Medications included in the propensity score matching were low-dose aspirin (B01AC06, B01AC30, N02BA01, N02BA51), NSAIDs (M01A except M01AX), 5-alpha reductase inhibitors (G04CB01, G04CB02), statins (C10AA, C10BA02), and SSRIs (N06AB).

Additionally, the comorbidity calculations included medication use as well as diagnoses codes. Specifically, diabetes mellitus (A10), COPD (R03BB) and alcohol related disease (N07BB).

Truven Cohort

Identification of medications in the Truven cohort was done by NDC number. Whereas the ATC codes used in the Danish registry include one code per drug, the NDC encodes the drug, dose, route, manufactory, and other information. As a result, the number of NDC numbers for each drug is much greater.

The NDC codes used in this study were identified by matching on the generic name in Thompson Reuters Red Book. They are:

Alfuzosin

00024420010, 00378500505, 00378500577, 13668002101, 13668002105, 13668002130, 13668002164, 16590027930, 24987020010, 24987020020, 29300015501, 29300015519, 31722030201, 31722030205, 33261099430, 35356028100, 42291011001, 42291011010, 47335095618, 47335095681, 47335095688, 54569557100, 54868504600, 54868504601, 54868504602, 54868632900, 57237011490, 59212020010, 60429034701, 60505285001, 61919034930, 64679073802, 64679073803, 65862024901, 68071080530, 69097084407, 69097084412, 76282030201, 76282030205

Doxazosin

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Terazosin

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Levodopa or carbidopa

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eTable 1. Cohort sample size by exclusion step

| Step | Denmark | | Truven | |
|---|--------------------|----------------------|--------------------|----------------------|
| | Number of TZ/DZ/AZ | Number of Tamsulosin | Number of TZ/DZ/AZ | Number of Tamsulosin |
| All newly started on med | 144,078 | 160,320 | 265,924 | 1,266,762 |
| At least 2 dispensing events within 1 st year of use | 89,503 | 100,496 | 185,801 | 1,070,358 |
| Age at least 40 | 87,704 | 99,211 | 180,693 | 598,353 |
| At least 1 year from RX start until censoring or event, free of event at RX start | 69,998 | 72,100 | 102,222 | 580,320 |
| Matched | 52,365 | 52,365 | 94,883 | 94,883 |

eTable 2. Demographic and baseline characteristics of the Danish cohort before and after matching

| | Unmatched | | | Matched | | |
|----------------------------|-------------------|-------------------|------|-------------------|-------------------|------|
| | TZ/DZ/AZ | Tamsulosin | SM D | TZ/DZ/AZ | Tamsulosin | SM D |
| N | 68,998 | 72,100 | | 52,365 | 52,365 | |
| Age | | | | | | |
| Median (IQR) | 68 (61-75) | 69 (62-76) | 0.06 | 68 (61-75) | 68 (61-75) | 0.00 |
| 40-59 years | 14,949 (21.7%) | 13,739 (19.1%) | 0.06 | 10,661 (20.4%) | 10,542 (20.1%) | 0.01 |
| 60-79 years | 44,830 (65.0%) | 47,970 (66.5%) | 0.03 | 34,912 (66.7%) | 34,938 (66.7%) | 0.00 |
| 80+ years | 9,219 (13.4%) | 10,391 (14.4%) | 0.03 | 6,792 (13.0%) | 6,885 (13.1%) | 0.01 |
| Use of drugs (current use) | | | | | | |
| Low-dose aspirin | 15,148 (22.0%) | 16,916 (23.5%) | 0.04 | 12,372 (23.6%) | 11,907 (22.7%) | 0.02 |
| Non-aspirin NSAIDs | 10,296 (14.9%) | 10,220 (14.2%) | 0.02 | 7,764 (14.8%) | 7,492 (14.3%) | 0.01 |
| 5a-reductase inhibitors | 3,716 (5.4%) | 5,206 (7.2%) | 0.08 | 2,736 (5.2%) | 2,865 (5.5%) | 0.01 |
| Statins | 13,140 (19.0%) | 16,845 (23.4%) | 0.11 | 11,709 (22.4%) | 11,289 (21.6%) | 0.02 |
| SSRIs | 3,541 (5.1%) | 4,101 (5.7%) | 0.02 | 2,930 (5.6%) | 2,721 (5.2%) | 0.02 |
| Diagnoses | | | | | | |
| Diabetes | 8,576 (12.4%) | 8,496 (11.8%) | 0.02 | 6,509 (12.4%) | 6,071 (11.6%) | 0.03 |
| COPD | 4,106 (6.0%) | 5,001 (6.9%) | 0.04 | 3,300 (6.3%) | 3,155 (6.0%) | 0.01 |
| HF | 2,404 (3.5%) | 2,545 (3.5%) | 0.02 | 1,910 (3.6%) | 1,788 (3.4%) | 0.01 |
| Alcohol-related disease | 1,891 (2.7%) | 1,992 (2.8%) | 0.00 | 1,479 (2.8%) | 1,395 (2.7%) | 0.01 |
| Charlson Comorbidity Index | | | | | | |
| 0 | 46,254 (67.0%) | 47,548 (65.9%) | 0.02 | 34,386 (65.7%) | 35,051 (66.9%) | 0.03 |
| 1-2 | 17,131 (24.8%) | 18,831 (26.1%) | 0.03 | 13,604 (26.0%) | 13,281 (25.4%) | 0.01 |
| 3 | 5,613 (8.1%) | 5,721 (7.9%) | 0.01 | 4,375 (8.4%) | 4,033 (7.7%) | 0.02 |
| Education | | | | | | |
| <=10 years | 22,051 (32.0%) | 23,375 (32.4%) | 0.01 | 16,730 (31.9%) | 16,563 (31.6%) | 0.01 |
| 11-12 years | 26,281 (38.1%) | 28,497 (39.5%) | 0.03 | 20,507 (39.2%) | 20,547 (39.2%) | 0.00 |
| 13+ years | 13,378 (19.4%) | 14,710 (20.4%) | 0.03 | 10,684 (20.4%) | 10,741 (20.5%) | 0.00 |
| Unknown | 7,288 (10.6%) | 5,518 (7.7%) | 0.10 | 4,444 (8.5%) | 4,514 (8.6%) | 0.00 |
| Other markers | | | | | | |
| No. of antihypertensives | | | | | | |

| | | | | | | |
|-----|-------------------|-------------------|------|-------------------|-------------------|------|
| 0 | 36,572 (53.0%) | 38,858 (53.9%) | 0.02 | 26,294 (50.2%) | 29,233 (55.8%) | 0.11 |
| 1-2 | 23,562 (34.1%) | 26,134 (36.2%) | 0.04 | 18,309 (35.0%) | 18,319 (35.0%) | 0.00 |
| 3-4 | 8,864 (12.8%) | 7,108 (9.9%) | 0.09 | 7,762 (14.8%) | 4,813 (9.2%) | 0.17 |

eTable 3. Demographic and baseline characteristics of the Truven cohort before and after matching

| | Unmatched | | | Matched | | |
|-------------------------------|--------------------|---------------------|-----------|--------------------|--------------------|-----------|
| | TZ/DZ/AZ | Tamsulosin | SMD | TZ/DZ/AZ | Tamsulosin | SMD |
| N | 102,222 | 374,014 | | 94,883 | 94,883 | |
| Age at RX Start (Years) | 64 (11.13) | 65 (11.45) | - 0.08 | 63.87 (11.06) | 63.89 (11.05) | 0.01 |
| Elixhauser CM (%) | | | | | | |
| Alcohol | 1,911 (1.87%) | 8,473 (2.27%) | - 0.02 | 1,790 (1.89%) | 1,848 (1.95%) | 0.00 |
| Anemia | 13,044 (12.76%) | 57,429 (15.35%) | - 0.05 | 12,034 (12.68%) | 12,193 (12.85%) | 0.00 |
| Blood Loss | 1,205 (1.18%) | 6,153 (1.65%) | - 0.03 | 1,115 (1.18%) | 1,122 (1.18%) | 0.00 |
| CHF | 7,988 (7.81%) | 37,666 (10.07%) | - 0.06 | 7,351 (7.75%) | 7,447 (7.85%) | 0.00 |
| Coagulopathy | 2,829 (2.77%) | 15,228 (4.07%) | - 0.05 | 2,574 (2.71%) | 2,620 (2.76%) | 0.00 |
| Depression | 6,625 (6.48%) | 32,365 (8.65%) | - 0.06 | 6,283 (6.62%) | 6,431 (6.78%) | 0.00 |
| DM | 28,607 (27.99%) | 103,548 (27.69%) | 0.00 | 26,467 (27.89%) | 26,816 (28.26%) | - 0.01 |
| DM with Complications | 10,685 (10.45%) | 37,553 (10.04%) | 0.01 | 9,691 (10.21%) | 9,974 (10.51%) | - 0.01 |
| Drug Abuse | 910 (0.89%) | 4,596 (1.23%) | - 0.02 | 856 (0.90%) | 880 (0.93%) | 0.00 |
| Fluid or Electrolyte Disorder | 9,908 (9.69%) | 44,255 (11.83%) | - 0.05 | 9,079 (9.57%) | 9,364 (9.87%) | - 0.01 |
| HIV | 337 (0.33%) | 1,073 (0.29%) | 0.01 | 315 (0.33%) | 328 (0.35%) | 0.00 |
| HTN | 69,004 (67.5%) | 233,480 (62.43%) | 0.08 | 62,726 (66.11%) | 63,993 (67.44%) | - 0.02 |
| HTN with Complications | 15,924 (15.58%) | 50,744 (13.57%) | 0.04 | 14,333 (15.11%) | 14,749 (15.54%) | - 0.01 |
| Hypothyroidism | 7,676 (7.51%) | 36,007 (9.63%) | - 0.05 | 7,270 (7.66%) | 7,344 (7.74%) | 0.00 |
| Liver Failure | 3,473 (3.40%) | 17,502 (4.68%) | - 0.05 | 3,308 (3.49%) | 3,402 (3.59%) | 0.00 |
| Lymphoma | 1,084 (1.06%) | 5,243 (1.40%) | - 0.02 | 1,021 (1.08%) | 1,053 (1.11%) | 0.00 |
| Metastatic Cancer | 1,115 (1.09%) | 7,176 (1.92%) | - 0.05 | 1,039 (1.10%) | 1,008 (1.11%) | 0.00 |
| Other Neuro Disorders | 5,652 (5.53%) | 33,423 (8.94%) | - 0.09 | 5,240 (5.52%) | 5,327 (5.61%) | 0.00 |
| Obesity | 7,446 (7.28%) | 32,361 (8.65%) | - 0.04 | 7,142 (7.53%) | 7,390 (7.79%) | - 0.01 |
| Paralysis | 1,495 (1.46%) | 8,414 (2.25%) | - 0.04 | 1,354 (1.43%) | 1,394 (1.47%) | 0.00 |
| Pulmonary Circ. Disease | 1,853 (1.81%) | 11,038 (2.95%) | - 0.05 | 1,694 (1.79%) | 1,769 (1.86%) | 0.00 |
| Psychoses | 5,247 (5.13%) | 25,591 (6.84%) | - 0.05 | 4,960 (5.23%) | 4,971 (5.24%) | 0.00 |
| Peptic Ulcer Disease | 237 (0.23%) | 1,283 (0.34%) | - 0.01 | 222 (0.23%) | 213 (0.22%) | 0.00 |

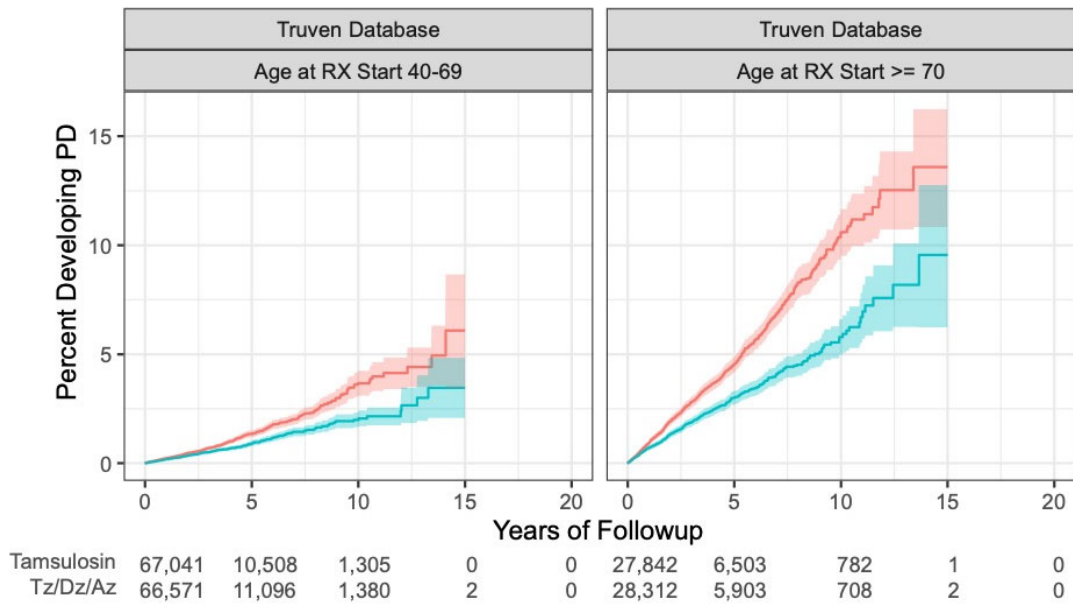
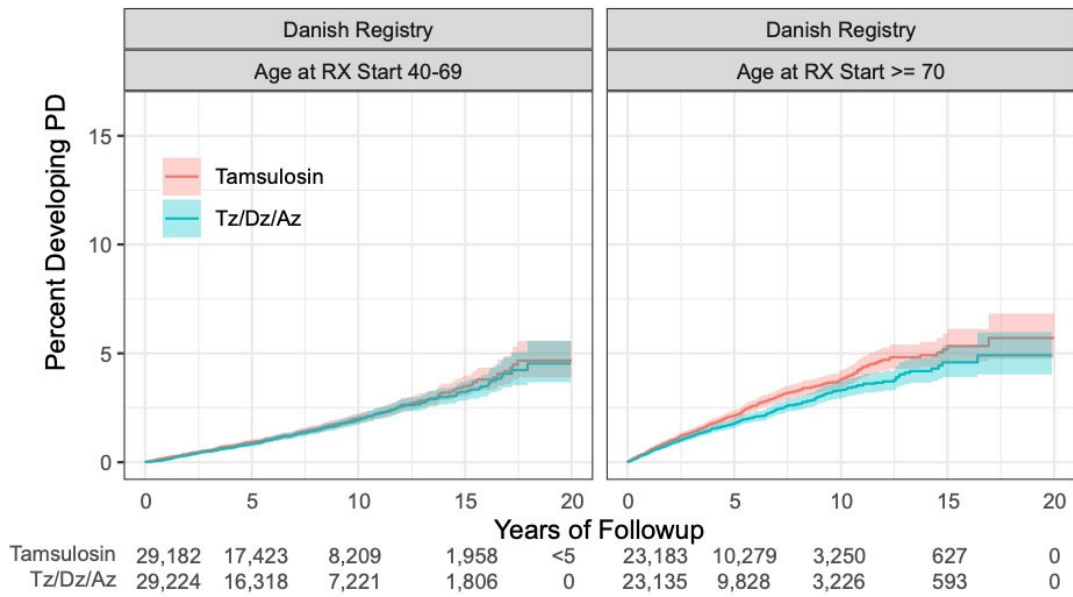
| | | | | | | |
|-----------------------------------|--------------------|--------------------|-----------|--------------------|--------------------|-----------|
| Chronic Pulmonary Disease | 19,833 (19.40%) | 92,021 (24.60%) | - 0.09 | 18,853 (19.87%) | 18,721 (19.73%) | 000 |
| Peripheral vascular disease | 12,592 (12.32%) | 59,378 (15.88%) | - 0.07 | 11,774 (12.41%) | 11,867 (12.51%) | 0.00 |
| Renal Failure | 8,631 (8.44%) | 25,094 (6.71%) | 0.05 | 7,471 (7.87%) | 7,924 (8.35%) | - 0.01 |
| RA | 3,884 (3.80%) | 18,850 (5.04%) | - 0.04 | 3,681 (3.88%) | 3,698 (3.90%) | 0.00 |
| Solid Tumor | 11,608 (11.36%) | 62,150 (16.62%) | - 0.11 | 11,095 (11.61%) | 10,846 (11.43%) | 0.01 |
| Valvular Disease | 11,693 (11.44%) | 57,109 (15.27%) | - 0.08 | 11,015 (11.61%) | 11,148 (11.75%) | 0.00 |
| Weight Loss | 2,521 (2.47%) | 15,705 (4.20%) | - 0.07 | 2,327 (2.45%) | 2,391 (2.52%) | 0.00 |
| RX Start Year | 2008.49 (3.71) | 2010.13 (3.95) | - 0.30 | 2008.73 (3.64) | 2008.88 (3.60) | - 0.03 |
| Mean Inpatient Days Per Year | 0.97 (5.45) | 1.70 (7.21) | - 0.08 | 0.89 (4.50) | 0.99 (4.35) | - 0.02 |
| Mean Inpatient Events Per Year | 0.18 (0.54) | 0.28 (0.66) | - 0.11 | 0.18 (0.51) | 0.18 (0.48) | - 0.01 |
| Outpatient Visits Per Year | 15.14 (16.04) | 17.24 (17.34) | - 0.09 | 15.07 (15.82) | 15.22 (14.76) | - 0.01 |
| Mean Years After Medication Start | 3.76 (2.67) | 3.71 (2.68) | 0.01 | 3.78 (2.65) | 3.78 (2.65) | 0.00 |

eTable 4. Typical doses and duration of therapy by drug

Values are median and interquartile ranges. Note that the total number of enrollees taking each of the AZ, DZ, TZ is greater than the number of people taking AZ/DZ/TZ because of switching between AZ, DZ, and TZ within the same enrollee.

| | Danish Cohort | | | | Truven Cohort | | | |
|---------------------------|------------------|--------------------|------------------|------------------|---------------|----------------|------------------|------------------|
| | TZ | DZ | AZ | Tamsulosin | TZ | DZ | AZ | Tamsulosin |
| Number | 2,879 | 15,501 | 33,981 | 52,365 | 37,144 | 38,747 | 24,179 | 94,883 |
| Total Defined Daily Doses | 475 (130, 1,481) | 1,044 (328, 2,426) | 706 (237, 1,920) | 780 (230, 1,920) | 252 (72, 720) | 345 (105, 870) | 520 (160, 1,200) | 450 (150, 1,020) |

eFigure 1. Kaplan-Meier survival curves stratified by age at medication start



eFigure 2. Log(-log[survival]) plots

If the hazards are proportional, these curves should not cross and should be parallel. Crossing and deviations from parallel lines early is less of an issue than late crossings or deviations. These lines appear relatively parallel and only cross during the very early data phase when the noise is larger than the signal. This suggests the proportional hazards assumption is reasonable.

