Additional file 3 Summary of patient characteristics of included studies

Table S1 Summary of patient characteristics of included interventional studies

Authors (Year)	**Recruitment**	**Sample size and age profile**	**Race/ethnicity in %**	**Men in %**	**BPH related scores (mean values)**	**Co-medication**	**Co-morbidities**
ALLHAT (2003) [47][1]	Practice based setting in the US only through (e.g.): · Universities or medical centers · Veterans Hospitals · Practices · Primary care · Specialty clinics	Doxazosin: · n=9,061 · ≥70 y: 3,092 Chlorthalidone: · n=15,255 · ≥70 y: 5,410	Chlorthalidone: · White: 47.2% · Black: 31.9% · Hispanic: 15.8% · Other: 5.1% Doxazosin: · White: 46.5% · Black: 32.9% · Hispanic: 16% · Other: 4.6%	Chlorthalidone: 53.0% Doxazosin: 53.6%	N.a.	Additional treatment for hypertension was allowed with: · Atenolol · Reserpine · Clonidine · Hydralazine	Comorbidities such as atherosclerotic cardiovascular disease, type 2 diabetes and unfavourable cholesterol levels were matched between the chlorthalidone and doxazosin group

Gotoh et al. (2005) [35][2]	Multicenter trial in JP through 17 urologists in 16 sites	Tamsulosin: · n=75 · mean age: 68.5 y · 95% CI: 67.0 – 70.1 y Naftopidil: · n=69 · mean age: 68.0 y · 95% CI: 66.4 – 69.8 y	N.a.	100%	Tamsulosin: · $V_{prostate}$: 33.6 ml · IPSS: 17.1 · QoL: 4.4 · PVR: 42.5 ml Naftopidil: · $V_{prostate}$: 29 ml · IPSS: 15.5 · QoL: 4.5 · PVR: 46.6 ml	Patients were excluded if they were currently in treatment with: · Antiandrogens · α1-antagonists · Anticholinergic drugs	Patients were excluded if they had (a history of) one or more of the following diseases: · Orthostatic hypertension · Neurological disease incl. bladder dysfunction · Carcinoma of bladder or prostate · Surgery for BPH or bladder neck obstruction · Urinary tract infections
Nishino et al. (2006) [36][3]	Patients of the Department of Urology at Gifu University (JP)	Tamsulosin/ naftopidil: · n=17 Naftopidil/ tamsulosin: · n=17	N.a.	100%	· $V_{prostate}$: 19.8 ml · IPSS: 20.4 · QoL: 4.9 · PVR: 54.1 ml · Q_{max}: 9.9 ml/s	Patients were excluded if they had ever been medically treated for BPH	Patients were excluded if they had (a history of) one or more of the following diseases (e.g.): · Neurogenic disorders · Urinary retention · Carcinoma of bladder · Urinary tract infections

Oelke et al. (2014) [48][4]	Patients were recruited internationally in 44 urology sites in Europe (71%), Mexico and Australia	Tamsulosin: · n=168 · ≥66 y: 72 Tadalafil: · n=171 · ≥66 y: 75 Placebo: · n=172 · ≥66 y: 77	Tamsulosin: · White: 78% · Black/African American: 0% · American Indian/Alaska Native: 22% Tadalafil: · White: 76% · Black/African American: 0.6% · American Indian/Alaska Native: 23.4% Placebo: · White: 76.2% · Black/African American: 0% · American Indian/Alaska Native: 23.8%	100%	Tamsulosin: · IPSS: 16.8 · Erectile dysfunction (ED): 69% · BMI: 27.9 kg/m² Tadalafil: · IPSS: 17.2 · ED: 70.8% · BMI: 27.1 kg/m² Placebo: · IPSS: 17.4 · ED: 69.8% · BMI: 28.1 kg/m²	Previous therapies within 12 mo prior to screening: Tamsulosin: · α-blockers: 25.6% · Other LUTS/BPH therapy: 5.4% · ED therapy: 12.5% Tadalafil: · α-blockers: 24% · Other LUTS/BPH therapy: 3.5% · ED therapy: 12.3% Placebo: · α-blockers: 26.2% · Other LUTS/BPH therapy: 4.7% · ED therapy: 13.4%	Patients excluded if they had (had) prostate cancer
Roehrborn (2006) [49][5]	Patients were recruited internationally in 148 urology sites in	Alfuzosin: · n=759 · ≥65 y: 449	N.a.	100%	Alfuzosin: · $V_{prostate}$: 46.9 ml · IPSS: 19.2 · PVR: 95.3 ml	Patients were excluded if they were taking medication which would eventually change the voiding pattern	Hypertension: · Alfuzosin: 36.1% · Placebo: 35%

	North America, Europe, Australia, Middle East and South-Africa	Placebo: · n=763 · ≥65 y: 439			· Q_{max}: 8.9 ml/s Placebo: · $V_{prostate}$: 46.6 ml · IPSS: 19.2 · PVR: 89 ml · Q_{max}: 8.8 ml/s		Patients were excluded if they had (a history of) one or more of the following diseases: · Postural hypotension or syncope · Carcinoma of prostate · Surgery of prostate · AUR
Yokoyama et al. (2011) [34][6]	Department of Urology at Kawasaki Medical School, Japan	Tamsulosin: · n=45 · mean age: 71.5 y Silodosin: · n=45 · mean age: 70.2 y Naftopidil: · n=46 · mean age: 69.1 y	N.a.	100%	Tamsulosin: · $V_{prostate}$: 32.5 ml · IPSS: 18 · QoL: 4.49 · PVR: 29.7 ml · Q_{max}: 8.56 ml/s Silodosin: · $V_{prostate}$: 33.3 ml · IPSS: 18.7 · QoL: 4.5 · PVR: 57.6 ml · Q_{max}: 9.03 ml/s Naftopidil: · $V_{prostate}$: 35 ml · IPSS: 17.4 · QoL: 4.55	N.a.	N.a.

					· PVR: 39.1 ml · Q_{max}: 8.63 ml/s		

[1] Patient characteristics refer to total study population including patients of all age groups ≥55 y.

[2] Patient characteristics refer to total study population including patients of all age groups ≥50 y with mean age (95% CI) being 68.5 y (67.0 y – 70.1 y)

[3] All patients are aged ≥66 y.

[4] Patient characteristics refer to total study population including patients of all age groups ≥45 y.

[5] Patient characteristics refer to total study population including patients of all age groups ≥55 y.

[6] Patient characteristics refer to total study population including patients of all age groups ≥50 y with mean age (SD) being 70.2 y (0.9), 71.5 y (1.1) and 69 y (1.2) for the silodosin, tamsulosin or nifedipine group, respectively.

Abbreviations: **BMI** = body mass index, **BPH** = benign prostatic hyperplasia, **ED** = erectile dysfunction, **IPSS =** international prostate symptom score, **N.a. =** not available, **PVR =** post-void residual urine, **Q_{max} =** maximum urinary flow rate, **QoL =** quality of life**, y** = years

Table S2 Summary of patient characteristics of included observational studies

Authors (Year)	**Recruitment**	**Sample size and age profile**	**Race/ethnicity in %**	**Men in %**	**Co-medication**	**Co-morbidities**
Retrospective Cohort Studies:						
Chrischilles et al. (2001) [50][1]	Cohorts were created from information received through a medical claims database in the US (1995-1997) including: · Outpatient drug utilization · Inpatient physician services · Outpatient physician services	Users: · n=1,564 · Mean age: 73 y · Prazosin=15 · Doxazosin=782 · Terazosin=839 Non-Users: · n=8,641 · Mean age: 72.5 y	N.a.	100%	Use of additional antihypertensive drugs (α1-blocker users vs. non-users): · Any agent: 56.3 % vs. 26.2% · ACE-inhibitors: 28.9% vs. 12.2% · Beta-blockers: 15.4% vs. 6.6% · Ca-Channel-blockers: 35.6% vs. 14.7% · Diuretics: 33.7% vs. 13.4% No. of agents used: · 0: 34.1% vs. 71.4% · 1: 30.2% vs. 14.3% · 2: 21.4% vs. 9.8% · >3: 14.2% vs. 4.6%	α1-blocker users vs. non-users: · Hypertension: 23% vs. 20.4% · Type 2 Diabetes: 8.2% vs. 7.1% · Cardiac arrhythmia: 8.3% vs. 7.2% No. of comorbidities: · 0: 62.7% vs. 66.3% · 1: 28.8% vs. 27.6% · 2: 7.4% vs. 5.0% · >3: 1.2% vs. 1.1%

Duan et al. (2018) [33][2]	Cohorts were created from US Medicare data (2006-2012) including 100% US Medicare beneficiaries	Tamsulosin: · n=253,136 No BPH-medication: · n=180,926 Doxazosin: · n=28,581 Terazosin: · n=23,858 Alfuzosin: · n=17,934 Dutasteride: · n=34,027 Finasteride: · n=38,767	Tamsulosin: · White: 86.7% · Black: 5.7% · Hispanic: 2.6% · Other: 5.1% No BPH medication: · White: 86.8% · Black: 5.6% · Hispanic: 2.5% · Other: 5.1%	100%	No. of drugs used (tamsulosin vs. no BPH medication): · 1-2: 29.2% vs. 29.2% · 3-4: 31.3% vs. 31.3.% · 5-6: 18.2% vs. 18.4% · ≥7: 8.7% vs. 8.6%	Tamsulosin vs. no BPH medication: · CeVD: 7.7% vs. 7.7% · PVD: 10.9% vs. 10.9% · CHF: 10.3% vs. 10.1% · Hypertension: 64.4% vs. 64.3% · Diabetes: 26.7% vs. 26.7% · Hyperlipidemia: 56.9% vs. 56.7% · Depression: 4.9% vs. 4.8%

Hiremath et al. (2019) [54][3]	Cohorts were derived from medical and administrative databases of Ontario, Canada (April 1st 1997 – March 31st 2015)	Matched cohorts: Alpha-1 antagonist users (terazosin, prazosin, doxazosin): · n=14,106 · Mean age: 75.7 y Other BP-lowering medication users: · n=14,106 · Mean age: 75.7 y	N.a.	0%, 100% women	High dimensional propensity score matching (limit ≥10%) between cohorts (α1-blocker users vs. other BP-lowering medication) with regard to : · Statins: 42.7% vs. 40.1% · Beta-blockers: 42.7% vs. 57.6% · ACE-inhibitors: 45.3% vs. 56.3% · Thiazide diuretics: 32% vs. 52.3% · Loop diuretics: 17.8% vs. 8.6% · Ca-channel-blockers: 65.3% vs. 65.8% · Antiarrhythmics: 1.1% vs. 0.9% · Clopidogrel: 3.1% vs. 2.6% · Antidiabetic medication: 28.4% vs. 26.8% · Antipsychotics: 3.1% vs. 2.7% · Nitrates: 6.6% vs. 6.6% · Clonidine: 1.3% vs. 0.5%	High dimensional propensity score matching (limit ≥10%) between cohorts (α1-blocker users vs. other BP-lowering medication) with regard to (e.g.): · Diabetes mell.: 41.1% vs. 40.0% · Ischemic stroke: 3.6% vs. 3.4% · Myocardial infarction: 1.4% vs. 1.4% · Cong. Heart failure: 8.9% vs. 6.8% · CAD: 16.5% vs. 16.7% · PVD: 3.2% vs. 2.5% · COPD: 4.5% vs. 3.7% · Arrhythmia: 6.4% vs. 6.1% · Major cancer: 9.9% vs. 9.5% · Fall: 8.8% vs. 8.4% · Facture: 7.6% vs. 7.4%
Hundemer et al. (2021) [32][3]	Cohorts were derived from medical and administrative databases of Ontario, Canada (2007 – 2015)	Matched cohorts: Alpha-1 antagonist users (terazosin, prazosin, doxazosin): · n=16,088 · Mean age: 75 y Other BP-lowering medication users:	N.a.	α1-blocker users: · 63% Other: · 62%	High dimensional propensity score matching (limit ≥10%) between cohorts (α1-blocker users vs. other BP-lowering medication) with regard to: No. of BP-lowering medications: · 1: 3% vs. 3% · 2: 11% vs. 11% · 3: 20% vs. 20% · 4: 31% vs. 31%	High dimensional propensity score matching (limit ≥10%) between cohorts (α1-blocker users vs. other BP-lowering medication) with regard to (e.g.): · Diabetes mell.: 55% vs. 55% · Ischemic stroke: 4% vs. 4% · Myocardial infarction: 5% vs. 7% · Cong. Heart failure: 16% vs. 19% · CAD: 32% vs. 34% · PVD: 3% vs. 3%

		· n=16,088 · Mean age: 75 y			· 5: 36% vs. 36% Other medication: · ARB: 32% vs. 28% · Ca-channel-blockers: 56% vs. 56% · Beta-blockers: 40% vs. 40% · Thiazide diuretics: 23% vs. 23% · Loop diuretics: 20% vs. 19% · Nitrate: 8% va. 11% · Clonidine: 1% vs. 0% · Antiarrhythmic: 2% vs. 2% · Clopidogrel: 65% vs. 66% · Statin: 65% vs. 66% · Antidiabetic medication: 40% vs. 40% · Antipsychotics: 4% vs. 3%	· COPD: 7% vs. 6% · Arrhythmia: 13% vs. 15% · Major cancer: 13% vs. 14%
Siemens et al. (2021) [55][3]	Cohorts were derived from medical and administrative databases of Ontario, Canada (2005 – 2015)	No medication: · n=69,988 · Mean age: 74 y Alpha-1 antagonist: · n=55,383 · Mean age: 74 y 5-ARI + alpha-1 antagonist:	N.a.	100%	N.a.	Baseline characteristics of cohorts (no medication / α1-blocker only / α1-blocker + 5-ARI combination): · Diabetes mell.: 9%/9%/9% · CVD: 3%/3%/3% · Myocardial infarction: 3%/4%/3% · Cong. Heart failure: 0%/0%/0% · PVD: 2%/2%/2%/ · COPD: 3%/3%/3%/ · Primary cancer: 5%/4%/3%

		· n=41,491 · Mean age: 74 y				
Tae et al. (2019) [56][3]	Cohorts were derived from the national health claims database of the Republic of Korea (January 1st, 2011 – December 31st, 2011)	Cohorts prior to matching: No medication: · n=3,336 · Mean age: 77 y Tamsulosin: · n=33,568 · Mean age: 76 y Doxazosin: · n=7,012 · Mean age: 77 y Terazosin: · n=9,443 · Mean age: 77 y	N.a.	100%	Prospensity score matching between cohorts with regard to the following therapies: · Antiplatelet · Anticoagulant · Statin · 5-ARI	Prospensity score matching between cohorts with regard to the following diagnoses: · Hypertension · Diabetes mellitus · Prior cancer history · Myocardial infaction · CHF · PVD · Renal disease

		Alfuzosin: · n=5,904 · Mean age: 76 y				
Welk et al. (2015) [51][3]	Cohorts were derived from administrative data provided by the province of Ontario, Canada	α1-blocker initiation: · n=147,084 No initiation: · n=147,084	n.a.	100%	Matched cohorts: unexposed (no α1-blocker use) vs. exposed (α1-blocker use): · Cancer: 22% vs. 20.5% · Cataract: 19.3% vs. 19% · CKD: 9.8% vs. 9.1% · Chronic lung disease: 28.1% vs. 28.1% · CHF: 14.1% vs. 13.3% · Coronary artery disease or angina: 42.9% vs. 42.4% · Dementia: 9.9% vs. 10.5% · Diabetes: 20.6% vs. 20.9% · Glaucoma: 6.8% vs. 6.5% · Hypertension: 69.8% vs. 69.4% · Osteoporosis: 6.1% vs. 6.0% · Prostate cancer: 13.0% vs. 11.7%	Matched cohorts: unexposed (no α1-blocker use) vs. exposed (α1-blocker use): · 5α-reductase inhibitors: 7.4% vs. 7.4% · ACE-inhibitors: 49.5% vs. 49.3% · Anti-inflammatory drugs: 15.8% vs. 16.8% · Antibiotics: 37.3% vs. 38.3% · Anticonvulsants: 5.0% vs. 5.1% · Antidepressants: 7.2% vs. 7.4% · Antineoplastic: 5.5% vs. 5.0% · Antiplatelets: 7.3% vs. 7.2% · Benzodiazepines: 14.2% vs. 14.4% · Beta-blockers: 32.3% vs. 30.9% · Bisphosphonates: 6.8% vs. 6.5% · Ca-channel blockers: 26.9% vs. 27.3% · Glucocorticoids: 9.6% vs. 9.5% · Inhaled acetylcholine: 7.5% vs. 7.6%

						· Inhaled beta-agonist: 13.3% vs. 12.8% · Inhaled corticosteroids: 6.0% vs. 5.5% · Narcotics: 19.2% vs. 19.4% · Non-potassium sparing diuretics: 26.4% vs. 23.8% · Potassium sparing diuretics: 4.2% vs. 3.6% · PPI: 25.9% vs. 25.4% · SSRI: 7.0% vs. 7.0% · Statins: 48.8% vs. 48.6%
Case-Control Studies:						
Hall and McMahon (2007) [52][4]	Cases and Controls were derived from data from the UK primary care records (THIN database)	Cases (fracture): · n=6,540 · Taking MR Doxazosin: 66 · Taking MR Doxazosin and ≥75y: 32 Controls (no fracture): · n=26,495 · Taking MR Doxazosin: 311	N.a.	100%	Cases (fractures) vs. controls (no fractures): · Thiazide diuretics: 14.5% vs. 17.1% · Other anti-hypertensives: 31.4% vs. 33.5% · Other cardiac drugs: 22.1% vs. 19.9% · Benzodiazepines: 9.8% vs. 7.3% · Antipsychotics: 6.2% vs. 3.6% · NSAIDs: 28.8% vs. 25.3% · Antidepressants: 16.1% vs. 10.3% · Oestrogen: 3.8% vs. 5.9% · Other osteoporosis treatment: 12.3% vs. 7.7%	Cases (fractures) vs. controls (no fractures): · Arthritis (excl. rheumatoid arthritis): 27.6% vs. 26.8% · Heart failure: 6.9% vs. 5.5% · COPD: 20.2% vs. 27.6% · Cerebrovascular accident: 10.9% vs. 8.6% · Osteoporosis: 8.0% vs. 4.8% · Type II diabetes: 8.9% vs. 7.9% · Dementia: 5.4% vs. 2.2%

		· Taking MR Doxazosin and ≥75y: 173			· Glucocorticoids: 8.4% vs. 6.0%	
Testa et al. (2018) [53][5]	Cases and Controls were enrolled in different settings in Italy including outpatient departments, nursing homes and acute care units	Syncopal fall: · n=354 · Mean age: 83.3 y Non-syncopal fall: · n=168 · Mean age: 83.9 y	N.a.	37.9%	Cases (syncopal fall) vs. controls (non-syncopal fall): · No. of antihypertensives (mean): 2.9 vs. 2.5 · < 2 antihypertensives: 50% vs. 56.4%	Cases (syncopal fall) vs. controls (non-syncopal fall): · Alzheimer's: 31.9% vs. 35.1% · Vascular dementia: 42.9% vs. 38.7% · Mixed dementia: 15.5% vs. 15.5% · Parkinson's: 5.6% vs. 6.5% · Hypertension: 74.3% vs. 75% · CAD: 19.5% vs. 18.5% · CHF: 8.5% vs. 10.1% · Atrial fibrillation: 25.1% vs. 23.8% · Stroke: 11.6% vs. 19.6% · TIA: 7.6% vs. 7.1% · Carotid atherosclerosis: 27.4% vs. 20.2% · Psychiatric disease: 33.6% vs. 29.2% · Diabetes: 20.9% vs. 24.4% · Dysthyroidism: 10.9% vs. 10.9%

[1] All patients are aged ≥65 y.

[2] Duan (2018) includes 6 cohort-pairs, all of which were prospensity-score-matched. The figures presented in this table only concern the biggest cohort with 161,729 people comparing tamsulosin-users vs. no BPH medication. All patients are aged ≥66 y.

[3] All patients are aged ≥66 y.

[4] Patient characteristics refer to total study population including patients of all age groups ≥50 y.

[5] All patients are aged ≥65 y.

Abbreviations: **5-ARI** = 5-alpha reductase inhibitor, **ARB** = angiotensin II receptor blockers, **CAD** = coronary artery disease, **COPD** = chronic obstructive pulmonary disease, **CVD** = cerebrovascular disease, **N.a.** = not available, **PVD** = peripheral vascular disease

Table S3 Summary of patient characteristics of included meta-analyses

Authors (Year)	**Data used**	**Patients**	**Race/ethnicity in %**	**Men in %**	**BPH related scores (mean values)**	**Co-medication**	**Co-morbidities**
Buzelin et al. (1997) [57][1]	Meta-analysis using raw data from two placebo-controlled studies conducted in 61 urological centers throughout Europe [56], 2nd study not published separately	SR alfzusosin: · n=292 · ≥65 y: 149 Placebo: · n=296 · ≥65 y: 153	N.a.	100%	Alfuzosin: · Boyarsky score: 9.4 · Q_{max}: 9.3 ml/s Placebo: · Boyarsky score: 9.6 · Q_{max}: 9.2 ml/s	Alfuzosin: · Antihypertensives: 30% Placebo: · Antihypertensives: 30%	Alfuzosin: · CVD: 43% · Hypertension: 29% Placebo: · CVD: 43% · Hypertension: 29%
Lowe (1994) [58][2]	Meta-analysis using raw data from six placebo-controlled trials, three conducted in the US (two of which two are unpublished) and three conducted in Europe [57-60]	Terazosin: · n=636 · ≥65 y: 285 Placebo: · n=360 · ≥65 y: 162	White: 94%	100%	N.a.	N.a.	N.a.

Chapple et al. (1997) [59]	Retrospective analysis of data from a meta-analysis [61] using raw data from two European multinational, multicentre, double-blind, placebo-controlled, randomized trials [62], 2nd study not published separately	Tamsulosin: · <65 y: 190 · ≥65 y: 191 Placebo: · <65 y: 93 · ≥65 y: 100	N.a.	100%	N.a.	Tamsulosin: · Antihypertensives/CV medication: 55/191 (29%) Placebo: · Antihypertensives/CV medication: 25/100 (25%)	Tamsulosin: · CVD: 69/191 (39%) · Hypertension: 46/186 (25%) Placebo: · CVD: 23/100 (23%) Hypertension: 22/97 (23%)

[1] Patient characteristics refer to total study population including patients of all age groups.

[2] Patient characteristics refer to total study population including patients of all age groups.

Abbreviations: **CV(D)** = cardiovascular (disease), **N.a.** = not available, $\mathbf{Q_{max}}$ **=** maximum urinary flow rate, **y** = years