Supplementary Materials

A Cohort definitions

In this study, we conduct all pairwise class-vs-class comparisons of the four drug classes, and specific pairwise drug-vs-drug comparisons of the highlighted rows in Table A1.

The cohort definitions for all drugs and classes are defined below.

** Index rule defining the index date: **

- First exposure to any drug or combination of drugs containing the RxNorm ingredient(s) of interest.

** Inclusion rules based on the index date:**

- At least 365 days of observation time prior to the index date
- No exposure to the target or comparator ingredient(s) before the index date
- No exposure to any other hypertension treatment on or before the index date
- A diagnosis of hypertension on or preceding the index date

Note that no prior or concurrent exposure to other hypertension treatments prior to or on the index date is allowed. For example, when comparing lisinopril to metoprolol, no prior exposure to hydrochlorothiazide or any other hypertension treatment is allowed, and lisinopril users are not allowed to initiate any other treatment at the time of initiating lisinopril. The end of the exposure cohort is defined as the end of the first exposure, allowing for 30-day gaps between consecutive prescriptions.

Table A1: Classes of interest and their corresponding drugs. All distinct classes are used in the class-vs-class comparisons. The blue highlight corresponds to drugs used in drug-vs-drug comparisons.

Drug	Class
Benazepril	ACE inhibitors
Captopril	ACE inhibitors
Enalapril	ACE inhibitors
Fosinopril	ACE inhibitors
Lisinopril	ACE inhibitors
Moexipril	ACE inhibitors
Perindopril	ACE inhibitors
Quinapril	ACE inhibitors
Ramipril	ACE inhibitors
Trandolapril	ACE inhibitors
Azilsartan	Angiotensin receptor blockers (ARBs)
Candesartan	Angiotensin receptor blockers (ARBs)
Eprosartan	Angiotensin receptor blockers (ARBs)
Irbesartan	Angiotensin receptor blockers (ARBs)
Losartan	Angiotensin receptor blockers (ARBs)
Olmesartan	Angiotensin receptor blockers (ARBs)
Telmisartan	Angiotensin receptor blockers (ARBs)
Valsartan	Angiotensin receptor blockers (ARBs)
Atenolol	Beta blockers - cardioselective
Betaxolol	Beta blockers - cardioselective
Bisoprolol	Beta blockers - cardioselective
Metoprolol	Beta blockers - cardioselective
Chlorthalidone	Thiazide or thiazide-like diuretics
Hydrochlorothiazide	Thiazide or thiazide-like diuretics
Indapamide	Thiazide or thiazide-like diuretics
Metolazone	Thiazide or thiazide-like diuretics

Table B2: Drugs of interest and their corresponding expected absolute systematic error (EASE) from pilot study on expected bias in Merative CCAE. The blue highlight corresponds to drugs used in drug-vs-drug comparisons in the primary study.

Target	Comparator	EASE	Target (N)	Comparator (N)
Metoprolol	Ramipril	0.420	1341616	123136
Ramipril	Losartan	0.465	137919	1447989
Metoprolol	Enalapril	0.437	1344988	123744
Enalapril	Losartan	0.515	133112	1448267
Ramipril	Chlorthalidone	0.439	139655	260038
Enalapril	Chlorthalidone	0.468	134931	260179
Atenolol	Chlorthalidone	0.453	401838	209553
Atenolol	Losartan	0.429	422552	1422942
Metoprolol	Olmesartan	0.288	1307576	457581
Hydrochlorothiazide	Metoprolol	0.278	2495081	1128586
Hydrochlorothiazide	Losartan	0.304	2387309	1099104
Bisoprolol	Losartan	0.278	95120	1450621
Metoprolol	Valsartan	0.274	1303963	593276
Telmisartan	Ramipril	0.300	134259	140271
Metoprolol	Lisinopril	0.208	1133383	2403583
Chlorthalidone	Olmesartan	0.248	249887	487747
Telmisartan	Enalapril	0.349	134992	135652
Valsartan	Ramipril	0.231	645486	137740
Valsartan	Enalapril	0.273	648017	133220
Lisinopril	Losartan	0.240	2531329	1155545
Bisoprolol	Chlorthalidone	0.228	100261	260502
Hydrochlorothiazide	Ramipril	0.229	2632349	125526
Metoprolol	Telmisartan	0.235	1349514	124714
Valsartan	Chlorthalidone	0.239	643671	248608
Bisoprolol	Enalapril	0.247	100908	135616

B Confounding

There exists a myriad of hypertension-related class-vs-class or drug-vs-drug comparisons. In this paper, only 4 drugs and 4 individual classes were selected. These selections were informed by findings from a prior pilot experiment, described here. We evaluated a large set of target-comparators to find pairs where bias (as measured through negative control outcomes) is large when not adjusting for any confounding. Because the overall study evaluates the performance of confounder adjustment methods, we selected comparisons exhibiting larger unadjusted bias. We selected treatments with adequate counts across all four available databases. We avoided treatments that were either newly introduced or long-established in order to maintain comparability and adequate sample size. These examples therefore represent scenarios with substantial confounding and to evaluate PS adjustment strategies on. "Bias" is defined via expected absolute systematic error (EASE). We compute EASE by first fitting an unadjusted cox model on all TCO tuples with a large set of negative controls, defined in Supplement C. Then, we estimate the empirical null distribution as $N(\mu, \sigma^2)$ using the effect estimates of a set of negative controls. EASE is defined as the mean for the empirical null distribution, and is insensitive to the spread of the null distribution.

Table B2 shows some of the highest EASE values in the database Merative CCAE for selected drug pairs.

C Negative controls

In our study, we use a set of real-world negative control outcomes generated by a data-rich algorithm for hypertensive drugs [1, 2]. Table C3 presents all of the negative controls used and their OMOP concept IDs.

Table C3: Negative control outcomes and their corresponding OMOP IDs.

Outcome Name	OMOP ID
Abnormal posture	439935
Abrasion and/or friction burn of multiple sites	443585
Anomaly of jaw size	45757682
Benign paroxysmal positional vertigo	81878
Cachexia	134765
Complication of gastrostomy	434675
Developmental delay	436077
Deviated nasal septum	377910
Epidermoid cyst	4170770
Foreign body in ear	374801
Galactosemia	439788
Ganglion cyst	40481632
Impacted cerumen	374375
Jellyfish poisoning	4265896
Lipid storage disease	4027782
Lymphangioma	433997
Marfan's syndrome	258540
Minimal cognitive impairment	439795
Nicotine dependence	4209423
Symbolic dysfunction	432436
Tooth loss	433244
Tracheostomy present	4201387
Abrasion and/or friction burn of trunk without infection	199192
Absence of breast	4088290
Acquired hallux valgus	75911
Acquired keratoderma	137951
Anal and rectal polyp	73241
Burn of forearm	133655
Calcaneal spur	73560
Changes in skin texture	140842
Chondromalacia of patella	81378
Cocaine abuse	432303
Complication due to Crohn's disease	46269889
Contact dermatitis	134438
Contusion of knee	78619
Crohn's disease	201606
Derangement of knee	76786
Disproportion of reconstructed breast	45757370
Endometriosis (clinical)	433527
Foreign body in orifice	259995
Hammer toe	433577
Hereditary thrombophilia	4231770

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Outcome Name	OMOP ID
Homocystinuria	4012934
Impingement syndrome of shoulder region	4344500
Ingrowing nail	139099
Injury of knee	444132
Late effect of contusion	434203
Late effect of motor vehicle accident	438329
Melena	4103703
Noise effects on inner ear	377572
Non-toxic multinodular goiter	136368
Postviral fatigue syndrome	4202045
Psychalgia	439790
Ptotic breast	81634
Regular astigmatism	380706
Senile hyperkeratosis	141932
Somatic dysfunction of lumbar region	36713918
Splinter of face without major open wound	443172
Sprain of ankle	81151
Tear film insufficiency	378427
Tobacco dependence syndrome	437264
Verruca vulgaris	140641
Wrist joint pain	4115367
Wristdrop	440193
Absent kidney	4092879
Bizarre personal appearance	4216219
Colostomy present	4201390
Exhaustion due to excessive exertion	437448
Feces contents abnormal	4092896
Foreskin deficient	4096540
Genetic disorder carrier	4168318
Inadequate sleep hygiene	40481897
Lagophthalmos	381021
Malingering	4051630
Mechanical complication of internal orthopedic device implant AND/OR graft	432798
Nonspecific tuberculin test reaction	40480893
Opioid abuse	438130
Opioid intoxication	4299094
Physiological development failure	437092
Poisoning by tranquilizer	433951
Social exclusion	4019836
Toxic effect of lead compound	436876
Toxic effect of tobacco and nicotine	440612
Unsatisfactory tooth restoration	45757285
Abnormal pupil	436409
Cannabis abuse	434327
Difficulty sleeping	4115402
Effects of hunger	433111
High risk sexual behavior	4012570
Kwashiorkor	432593

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Outcome Name	OMOP ID
Macular drusen	4083487
Passing flatus	4091513
Presbyopia	373478
Strain of rotator cuff capsule	72748
Acanthosis nigricans	4299544
Acute conjunctivitis	376707
Acute tonsillitis	24660
Adhesive capsulitis of shoulder	77644
Alcoholism	4218106
Allergic rhinitis	257007
Blepharitis	378425
Bronchiectasis	256449
Burping	4152350
Callosity	4067069
Candidiasis of skin	4172458
Cannabis dependence	440387
Carpal tunnel syndrome	380094
Cerebral palsy	4134120
Cervical radiculopathy	137548
Chalazion	381581
Chronic obstructive lung disease	255573
Costal chondritis	4272340
Coxsackie virus disease	436027
Cystic fibrosis	441267
Cyst of ovary	197610
Dental caries	133228
Disease due to Papilloma virus	4147672
Dislocation of shoulder joint	4213373
Dysplasia of cervix	192367
Epicondylitis	4249170
Genital herpes simplex	74855
Gout	440674
Hemochromatosis	4163735
Hemorrhoids	195562
Hordeolum	4265426
Human papilloma virus infection	441788
Hydrocele of testis	4131791
Hyperlipidemia	432867
Hyperosmolality and or hypernatremia	441829
Hypoparathyroidism	140362
Infection AND/OR inflammatory reaction due to internal prosthetic device implant AND/OR graft	440276
Influenza	4266367
Laceration of perineum	4152967
Lateral epicondylitis	81379
Low back pain	194133
Ménière's disease	79833
Metabolic syndrome X	436940
Non-toxic uninodular goiter	134898

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Outcome Name	OMOP ID
Obstruction of urethra	4318847
Onychomycosis due to dermatophyte	140648
Osteoarthritis of knee	4079750
Osteoporosis	80502
Overactive bladder	37206607
Parkinson's disease	381270
Perforation of tympanic membrane	375292
Plantar fasciitis	4002650
Pneumothorax	253796
Prolapse of intestine	4295888
Prostatitis	194997
Ptosis of eyelid	374044
Radial styloid tenosynovitis	73300
Sciatica	372409
Sickling disorder due to hemoglobin S	4213628
Sleep apnea	313459
Solitary nodule of lung	4142875
Tinea pedis	133141
Type 1 diabetes mellitus without complication	443412
Ureteric stone	201916
Uterine prolapse	4092565
Vitamin D deficiency	436070

D Covariate choice

In this study, the Health Analytics Data-to-Evidence Suite (HADES)[3] package `FeatureExtraction` is utilized to generate features (predictors) for the model [4]. Standard features typically take binary format that indicate whether a given patient had a certain condition (SNOMED), drug (RXNorm), or other OMOP-CDM standardized vocabularies during the observation time before the population index date. Many vocabularies have hierarchical structures; for example, a SNOMED code for condition "heart disease" has children codes "chronic heart disease," "acute heart disease," etc., that are more specific versions of the initial parent code. FeatureExtraction "rolls up" vocabulary codes using this hierarchy for conditions and drugs when selecting features of interest. This study uses the following features in the LSPS models:

Short-term features occurring between -30 days and 0 days relative to index and long-term features occurring between -365 days and 0 days relative to index:

- Observations
- Conditions (rolled up using hierarchy)
- Drugs (rolled up into ingredients using hierarchy) excluding the ingredients in Table D4
- Visit type
- Measurements
- Procedures
- Devices

Demographic information:

- Index month
- Ethnicity
- Age group (5 year bins)

- Race
- Gender

Medical scores using all conditions prior to window end:

- Diabetes Comorbidity Severity Index (DCSI)
- CHADS2
- CHADS2VASc

We screen out features with < 0.1 incidence rate, leaving each analysis with roughly $15,000$ predictors.

Table D4: Excluded drug ingredients and their corresponding OMOP IDs.

Ingredient	OMOP ID
acebutolol	1319998
aliskiren	1317967
amiloride	991382
amlodipine	1332418
atenolol	1314002
azilsartan	40235485
benazepril	1335471
betaxolol	1322081
bisoprolol	1338005
bumetanide	932745
candesartan	1351557
captopril	1340128
carvedilol	1346823
chlorthalidone	1395058
clonidine	1398937
diltiazem	1328165
doxazosin	1363053
enalapril	1341927
eplerenone	1309799
eprosartan	1346686
felodipine	1353776
fosinopril	1363749
furosemide	956874
guanfacine	1344965
hydralazine	1373928
hydrochlorothiazide	974166
indapamide	978555
irbesartan	1347384
isradipine	1326012
labetalol	1386957
lisinopril	1308216
losartan	1367500
methyldopa	1305447
metolazone	907013
metoprolol	1307046
minoxidil	1309068
moexipril	1310756
nadolol	1313200
nebivolol	1314577
nicardipine	1318137
nifedipine	1318853
nisoldipine	1319880
olmesartan	40226742
penbutolol	1327978

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Ingredient	OMOP ID
perindopril	1373225
pindolol	1345858
prazosin	1350489
propranolol	1353766
quinapril	1331235
ramipril	1334456
spironolactone	970250
telmisartan	1317640
terazosin	1341238
torsemide	942350
trandolapril	1342439
triamterene	904542
valsartan	1308842
verapamil	1307863

References

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