

## Supplementary Online Content

Fralick M, Kesselheim AS, Avorn J, Schneeweiss S. Use of health care databases to support supplemental indications of approved medications. *JAMA Intern Med*. Published online November 20, 2017. doi:10.1001/jamainternmed.2017.3919

**eTable 1.** Covariate Definitions

**eTable 2.** Additional Baseline Characteristics

**eAppendix.** Methodology for Selecting Telmisartan

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

**eTable 1. Covariate definitions**

<b>Covariate</b>	<b>Description</b>
Obese	278.00, 649.1, 649.10, 649.11, 649.12, 649.13, 649.14, 649.2, 649.20, 649.21, 649.22, 649.23, 649.24, V85.3, V85.30, V85.31, V85.32, V85.33, V85.34, V85.35, V85.36, V85.37, V85.38, V85.39, V85.4, V85.41, V85.42, V85.43, V85.44, V85.45, 539, 539.0, 539.01, 539.09, 539.8, 539.81, 539.89  OR  Any of: ORLISTAT, PHENTERMINE HCL, PHENTERMINE HCL/TOPIRAMATE, DIETHYLPROPION HCL, PHENDIMETRAZINE TARTRATE, BENZPHETAMINE HCL, SIBUTRAMINE HCL M-HYDRATE HCPCS/PROC_CD Procedure Code is any of: 43644, 43645, 43770, 43842, 43843, 43845, 43846, 43847, 43999
Smoking	V15.82, 305.1x, 649.0x, 989.84 OR use of varenicline tartrate or nicotine replacement therapy OR CPT code 99406, 99407, S9075, S9453
<b>Diabetes severity</b>	
Diabetes mellitus without mention of complications	250.0x
Diabetic nephropathy	250.4x, 583.81
Diabetic neuropathy	250.6x, 357.2x
Diabetes with peripheral circulatory disorders	250.7x
Diabetes with unspecified complications	250.9, 250.90, 250.92
<b>Other comorbidities</b>	
Hypertension	401.xx-405.xx
Hyperlipidemia	272.0, 272.2, 272.4
Congestive heart failure	428.xx, 398.91, 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93
Ischemic heart disease	410.xx-411.0, 411.81, 412 429.7,414*
Acute myocardial infarction	410*, 411.0, 411.81
Angina	413.** 411.**
History of coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI)	36.1* 36.2, 33510, 33511, 33512, 33513, 33514, 33516, 33517, 33518, 33519, 33520, 33521, 33522, 33523, 33530, 33534, 33534, 33536, 33545, 33572  36.01, 36.02, 36.03, 36.05, 36.09  92920, 92921, 92924, 92925, 92937, 92938, 92941, 92943, 92944, 92973, 92982, 92984, 92995, 92996 00.66 V45.82
Peripheral vascular disease	440.20 - 440.24, 440.29 – 440.32, 440.3, 443.9
Atrial fibrillation	427.3x
Ischemic stroke	433.x1, 434.x1, 434.9, 436.xx

Hemorrhagic stroke	430.xx, 431.xx
Transient ischemic attack (TIA)	435.xx (not 435.2)
Chronic obstructive pulmonary disease	491.xx, 492.xx, or 496.xx
Asthma	493.xx
Obstructive sleep apnea	327.23
Pneumonia	480.xx – 486.xx, 487.0x, 507.xx
Other renal disease (non-diabetic)	580.xx-587.xx, 403.xx, 404.xx, 572.4x, 791.2x, 791.3x, 274.10, 440.1x, 442.1x, 453.3x, 593.xx, 753.0x, 753.3x, 866.00, 866.01, 866.1x,
Sepsis/Septicemia	995.91, 995.92, 038.xx
Osteoarthritis	715.xx
Depression	293.83, 296.2x, 296.3x, 298.0x, 300.4x, 309.0x, 309.1x, 309.28, 311.xx
Anxiety	293.84, 300.0x, 300.2x, 300.3x, 309.24, 308.0x, 309.81
Sleep disorder	307.4x, 327.0x, 327.2x 780.5x, 347.xx
Dementia (and related)	290.xx, 294.xx, 330.xx, 331.xx
Urinary incontinence	788.3x, 788.91
<b>Other medications</b>	
Angiotensin converting enzyme inhibitors (ACE)	Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril
Angiotensin receptor blocker (ARB)	Azilsartan, candesartan, eprostatan, irbesartan, losartan, olmesartan, telmisartan, valsartan
Beta blockers	Acebutolol, atenolol, betaxolol, bisoprolol, carteolol, carvedilol, esmolol, labetalol, metoprolol tartrate, metoprolol succinate, propranolol, penbutolol, pindolol, nadolol, nebivolol, sotalol, timolol
Calcium channel blockers	Diltiazem Mibefradil Verapamil Amlodipine Clevidipine Bepridil Felodipine Isradipine Nicardipine Nifedipine Nimodipine Nisoldipine Amlodipine–atorvastatin
Thiazides	Bendroflumethiazide Chlorothiazide Chlorthalidone Hydrochlorothiazide Hydroflumethiazide Indapamide Methyclothiazide Metolazone Polythiazide Trichlormethiazide
Loop diuretics	furosemide, bumetanide, torsemide, ethacrynic acid
Other diuretics	Amiloride, eplerenone, spironolactone, triamterene
Nitrates	Nitroglycerin, isosorbide dinitrate, isosorbide mononitrate
Digoxin	Digoxin
Antiarrhythmics	Amiodarone, dronedarone, flecainide, ibutilide, procainamide, propafenone, quinidine disopyramide, dofetilide, mexiletine, moricizine, tocainide
COPD/asthma meds	Fluticasone/salmeterol, budesonide/formoterol, mometasone/formoterol, arformoterol, formoterol, salmeterol, albuterol, levalbuterol, metaproterenol, pirbuterol, terbutaline, ipratropium, tiotropium, theophylline, montelukast, zafirlukast, zileuton
Statins	Atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin, rosuvastatin, lovastatin–niacin, ezetimibe–simvastatin, pravastatin- aspirin, pitavastatin
Other lipid-lowering drugs	Niacin Niacinamide Fenofibrate Gemfibrozil Cholestyramine Colestipol Ezetimibe
Oral anticoagulant	Warfarin, dabigatran, rivaroxaban, apixaban
Heparins	Heparin, dalteparin, enoxaparin, tinzaparin
Antiplatelets	Aspirin, clopidogrel, prasugrel, ticlopidine, aspirin–dipyridamole, dipyridamole alone, cilostazol, ticagrelor
NSAIDs	Diclofenac etodolac flurbiprofen ketorolac ibuprofen indomethacin meloxicam naproxen piroxicam sulindac
Cox-2 inhibitors	Celecoxib Rofecoxib valdecoxib
Opioids (and related)	Codeine Fentanyl Hydrocodone Hydromorphone Meperidine Morphine Oxycodone Propoxyphene Oxymorphone Tramadol

Oral steroids	Cortisone hydrocortisone prednisone prednisolone methylprednisolone triamcinolone dexamethasone, bethamethasone
Antidepressants	Paroxetine Citalopram Escitalopram Fluoxetine Fluvoxamine Sertraline Venlafaxine Desvenlafaxine Levomilnacipran Duloxetine Amitriptyline Amoxapine Clomipramine Desipramine Doxepin Imipramine Maprotiline Nortriptyline Protriptyline Trimipramine Bupropion Mirtazapine Nefazodone Trazodone Phenelzine Isocarboxazid Tranylcypromine Vilazodone, Vortioxetine
Anticonvulsants	carbamazepine, divalproex, eslicarbazepine, ethotoin, ethosuximide, ezogabine, felbamate, fosphenytoin, gabapentin, lacosamide, lamotrigine, levetiracetam, mephenytoin, mephobarbital, methsuximide, oxcarbazepine, perampanel, phenobarbital, phenytoin, pregabalin, primidone, rufinamide, tiagabine, topiramate, valproic acid, vigabatrin, zonisamide
Antipsychotics	clozapine risperidone olanzapine quetiapine aripiprazole ziprasidone chlorpromazine fluphenazine mesoridazine perphenazine promazine thioridazine trifluoperazine triflupromazine haloperidol loxapine molindone pimozide thiothixene asenapine iloperidone lurasidone paliperidone pimozide propiomazine triflupromazine
Benzodiazepines	Alprazolam Chlordiazepoxide Clonazepam Clorazepate Diazepam Estazolam Flurazepam Halazepam Lorazepam Midazolam Oxazepam Quazepam Temazepam Triazolam
Use of anxiolytics/hypnotics	Eszopiclone Zaleplon Zolpidem Chloral hydrate Diphenhydramine Doxylamine Ethchlorvynol Glutethimide Methaqualone buspirone hydroxyzine meprobamate
Antiparkinsonian meds	Benzotropine biperiden procyclidine trihexyphenidyl tolcapone amantadine levodopa pergolide pramixepole ropinirole rotigotine carbidopa/levodopa rasagiline
Bisphosphonates	zoledronic acid alendronate sodium alendronate sodium/cholecalciferol (vitamin d3) etidronate disodium ibandronate sodium risedronate sodium risedronate sodium/calcium carbonate pamidronate disodium
<b>Health care utilization</b>	
Emergency department visits	Any visit to an emergency room or urgent care clinic
Visits to primary doctors (internal medicine/family medicine)	0311, 0312, 0313, 0314, 0316, 0317, 0318, 0319, 0326, 0327, 0329, 0330, 0331, 0332, 0333, 0334, 0335, 0336, 0337, 0338, 0339, 0340, 0341, 0342, 1046, 1113, 1127, 1133, 1419, 1423, 1643, 1646, 1661, 1673, 1694, 1697, 1719, 1721, 1726, 1743, 1755, 1764, 1785, 1790, 1791, 1832, 1854, 1860, 1864, 1865, 1903, 1927, 1940, 2050, 2068, 2073, 2189, 2208, 2219, 2228, 2233, 2249, 2254, 2280, 2286, 2313, 2314, 2324, 2340, 2354, 2359, 2373, 2375, 2378, 2384, 2392, 2403, 2446, 2485, 2574, 2607, 2610, 2613, 2614, 2615, 2628, 2644, 2677, 2736, 2790, 2811, 2826, 2835, 2837, 2842, 2889, 2904, 2930, 2978, 2996, 3122, 3150, 3241, 3268, 3350, 3531, 3564, 3765, 3777, 3812, 4135  240,204,825,845
Total N distinct pharmacological agents prescribed	Includes generic and brand name medications and also includes some over the counter medications
<b>Diagnostics</b>	
Preventive services	Prostate specific antigen test: 84153, 84152 – 84154, G0103  Colonoscopy 45378 45379 45380 45381 45382 45383 45384 45385 45386 45387 45388 45389 45390 45391 45392 G0105 45.23 Fecal occult blood test G0107 G0328 82270 82274  Flu shot: 90655 – 90660 90724 G0008 V04.8 V04.81 V06.6
Hemoglobin A1C	83036

Creatinine	82565
Number of tests for comprehensive metabolic panels	80053
Thyroid function	84436, 84439, 84443, 84479, 80091, 80092
ECHO	88.72, 00.24, 93306, 93307, 93308, 93312-93318, 93320, 93321, 93350, 93351, 93355, 93662
<b>OUTCOME</b>	
Stroke	Inpatient ICD-9 discharge diagnosis: 430.xx Subarachnoid hemorrhage (SAH) 431.xx Intracerebral hemorrhage (ICH) 433.x1 Occlusion and stenosis of precerebral arteries with cerebral infarction 434.x1 Occlusion and stenosis of cerebral arteries with cerebral infarction 436.x Acute, but ill-defined cerebrovascular events
Heart failure	Inpatient ICD-9 diagnosis 428.x, 398.91, 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93
Myocardial infarction	Inpatient ICD-9 Dx 410.X (acute myocardial infarction)
Angioedema	277.6 995.1

5 digit codes (e.g., 88053) represent Current Procedural Terminology (CPT) or Healthcare Common Procedure Coding (HCPC). The remaining codes are generally International Classification of Disease – 9<sup>th</sup> revision codes (ICD9).

eTable 2. Additional baseline Characteristics.

Variable	Unmatched population			Propensity-score matched population		
	Ramipril (N=48,053)	Telmisartan (N=4665)	SD	Ramipril (N=4665)	Telmisartan (N=4665)	SD
Quarter of Cohort Entry Date			0.046			0.053
...First Quarter	13,667 (28.4%)	1,198 (25.7%)		1,149 (24.6%)	1,198 (25.7%)	
...Second Quarter	10,080 (21.0%)	1,038 (22.3%)		1,005 (21.5%)	1,038 (22.3%)	
...Third Quarter	12,730 (26.5%)	1,310 (28.1%)		1,395 (29.9%)	1,310 (28.1%)	
...Fourth Quarter	11,576 (24.1%)	1,119 (24.0%)		1,116 (23.9%)	1,119 (24.0%)	
Mean age			0.119			0.007
	68.29 (9.52)	69.43 (9.60)		69.36 (9.67)	69.43 (9.60)	
Sex			0.303			0.03
...Male	31,940 (66.5%)	2,413 (51.7%)		2,343 (50.2%)	2,413 (51.7%)	
...Female	16,113 (33.5%)	2,252 (48.3%)		2,322 (49.8%)	2,252 (48.3%)	
Asthma	1,586 (3.3%)	195 (4.2%)	0.046	173 (3.7%)	195 (4.2%)	0.024
Angina	11,272 (23.5%)	815 (17.5%)	0.149	817 (17.5%)	815 (17.5%)	0.001
Chronic obstructive pulmonary disease	2,064 (4.3%)	155 (3.3%)	0.051	162 (3.5%)	155 (3.3%)	0.008
Type 2 diabetes mellitus	14,375 (29.9%)	1,524 (32.7%)	0.059	1,514 (32.5%)	1,524 (32.7%)	0.005
Digoxin	2,863 (6.0%)	240 (5.1%)	0.036	231 (5.0%)	240 (5.1%)	0.009
Heart failure	7,205 (15.0%)	510 (10.9%)	0.121	526 (11.3%)	510 (10.9%)	0.011
Obese	620 (1.3%)	61 (1.3%)	0.002	66 (1.4%)	61 (1.3%)	0.009
Dementia	1,511 (3.1%)	148 (3.2%)	0.002	153 (3.3%)	148 (3.2%)	0.006
Renal disease (non-diabetic)	3,549 (7.4%)	545 (11.7%)	0.147	515 (11.0%)	545 (11.7%)	0.02
Acute myocardial infarction	3,587 (7.5%)	147 (3.2%)	0.193	146 (3.1%)	147 (3.2%)	0.001
Anxiety	806 (1.7%)	111 (2.4%)	0.05	108 (2.3%)	111 (2.4%)	0.004
Ischemic heart disease	37,591 (78.2%)	3,105 (66.6%)	0.263	3,053 (65.4%)	3,105 (66.6%)	0.024
Obstructive sleep apnea	84 (0.2%)	10 (0.2%)	0.009	12 (0.3%)	10 (0.2%)	0.009
A1C ordering	7,449 (15.5%)	784 (16.8%)	0.035	767 (16.4%)	784 (16.8%)	0.01
Depression	1,843 (3.8%)	192 (4.1%)	0.014	207 (4.4%)	192 (4.1%)	0.016
Diabetes with peripheral circulatory disorders	948 (2.0%)	116 (2.5%)	0.035	135 (2.9%)	116 (2.5%)	0.025
Diabetes with unspecified complications	485 (1.0%)	49 (1.1%)	0.004	53 (1.1%)	49 (1.1%)	0.008
Diabetic Nephropathy	130 (0.3%)	22 (0.5%)	0.033	19 (0.4%)	22 (0.5%)	0.01
Emergency room visit	9,946 (20.7%)	907 (19.4%)	0.031	911 (19.5%)	907 (19.4%)	0.002
Fecal Occult Blood Test	1,996 (4.2%)	176 (3.8%)	0.02	184 (3.9%)	176 (3.8%)	0.009
Flu Shot	4,141 (8.6%)	401 (8.6%)	0.001	392 (8.4%)	401 (8.6%)	0.007
Hyperlipidemia	16,514 (34.4%)	1,548 (33.2%)	0.025	1,545 (33.1%)	1,548 (33.2%)	0.001
Hemorrhagic Stroke	268 (0.6%)	28 (0.6%)	0.006	32 (0.7%)	28 (0.6%)	0.011
Hypertension	21,361 (44.5%)	2,835 (60.8%)	0.331	2,832 (60.7%)	2,835 (60.8%)	0.001
Ischemic stroke	4,352 (9.1%)	478 (10.2%)	0.04	550 (11.8%)	478 (10.2%)	0.049
Diabetic Neuropathy	1,495 (3.1%)	165 (3.5%)	0.024	169 (3.6%)	165 (3.5%)	0.005
Prostate specific antigen test	5,246 (10.9%)	434 (9.3%)	0.054	408 (8.7%)	434 (9.3%)	0.019

Retinopathy	2,186 (4.5%)	280 (6.0%)	0.065	290 (6.2%)	280 (6.0%)	0.009
Thyroid function test	6,292 (13.1%)	694 (14.9%)	0.051	667 (14.3%)	694 (14.9%)	0.016
Metabolic panel	11,147 (23.2%)	1,124 (24.1%)	0.021	1,104 (23.7%)	1,124 (24.1%)	0.01
Osteoarthritis	694 (1.4%)	67 (1.4%)	0.001	64 (1.4%)	67 (1.4%)	0.005
Peripheral Vascular Disease	2,651 (5.5%)	362 (7.8%)	0.09	355 (7.6%)	362 (7.8%)	0.006
Pneumonia	2,525 (5.3%)	179 (3.8%)	0.068	162 (3.5%)	179 (3.8%)	0.019
Sepsis	503 (1.0%)	36 (0.8%)	0.029	27 (0.6%)	36 (0.8%)	0.024
Sleep disorder	2,461 (5.1%)	316 (6.8%)	0.07	330 (7.1%)	316 (6.8%)	0.012
Urinary incontinence	406 (0.8%)	70 (1.5%)	0.061	72 (1.5%)	70 (1.5%)	0.004
Smoking	1,734 (3.6%)	115 (2.5%)	0.067	128 (2.7%)	115 (2.5%)	0.017
Anti-platelets	11,031 (23.0%)	1,127 (24.2%)	0.028	1,148 (24.6%)	1,127 (24.2%)	0.01
Antiarrhythmics	1,851 (3.9%)	148 (3.2%)	0.037	152 (3.3%)	148 (3.2%)	0.005
Anticonvulsants	3,514 (7.3%)	457 (9.8%)	0.089	468 (10.0%)	457 (9.8%)	0.008
Antidepressants	8,468 (17.6%)	950 (20.4%)	0.07	954 (20.5%)	950 (20.4%)	0.002
Antiparkinson's medications	872 (1.8%)	136 (2.9%)	0.072	119 (2.6%)	136 (2.9%)	0.022
Antipsychotics	741 (1.5%)	73 (1.6%)	0.002	78 (1.7%)	73 (1.6%)	0.008
Benzodiazepines	6,112 (12.7%)	748 (16.0%)	0.095	763 (16.4%)	748 (16.0%)	0.009
Anxiolytics/hypnotics	3,763 (7.8%)	427 (9.2%)	0.047	410 (8.8%)	427 (9.2%)	0.013
Beta blockers	20,957 (43.6%)	1,926 (41.3%)	0.047	1,913 (41.0%)	1,926 (41.3%)	0.006
Bisphosphonates	2,257 (4.7%)	319 (6.8%)	0.092	342 (7.3%)	319 (6.8%)	0.019
COPD/asthma meds	7,150 (14.9%)	812 (17.4%)	0.069	817 (17.5%)	812 (17.4%)	0.003
Cox-2 inhibitors	3,435 (7.1%)	319 (6.8%)	0.012	307 (6.6%)	319 (6.8%)	0.01
Creatinine test	2,091 (4.4%)	223 (4.8%)	0.021	219 (4.7%)	223 (4.8%)	0.004
Heparins	371 (0.8%)	38 (0.8%)	0.005	38 (0.8%)	38 (0.8%)	0
Nitrates	9,804 (20.4%)	814 (17.4%)	0.075	807 (17.3%)	814 (17.4%)	0.004
NSAIDs	4,442 (9.2%)	526 (11.3%)	0.067	533 (11.4%)	526 (11.3%)	0.005
Opioids	11,894 (24.8%)	1,299 (27.8%)	0.07	1,288 (27.6%)	1,299 (27.8%)	0.005
Oral anticoagulants	4,623 (9.6%)	426 (9.1%)	0.017	405 (8.7%)	426 (9.1%)	0.016
Oral steroids	4,554 (9.5%)	487 (10.4%)	0.032	472 (10.1%)	487 (10.4%)	0.011
Other lipid lowering drugs	4,917 (10.2%)	484 (10.4%)	0.005	457 (9.8%)	484 (10.4%)	0.019
Atrial fibrillation	5,499 (11.4%)	427 (9.2%)	0.075	423 (9.1%)	427 (9.2%)	0.003
Total number of meds			0.096			0.025
...mean (Sdev)	1.98 (2.16)	2.19 (2.25)		2.13 (2.19)	2.19 (2.25)	
Cardiologist visit	29,928 (62.3%)	2,526 (54.1%)	0.165	2,585 (55.4%)	2,526 (54.1%)	0.025
Internal Medicine/Family	35,314 (73.5%)	3,571 (76.5%)	0.071	3,573 (76.6%)	3,571 (76.5%)	0.001
Echo	19,496 (40.6%)	1,589 (34.1%)	0.135	1,638 (35.1%)	1,589 (34.1%)	0.022
Age category			0.149			0.031
55-59	9,747 (20.3%)	802 (17.2%)		839 (18.0%)	802 (17.2%)	
60-64	11,539 (24.0%)	985 (21.1%)		947 (20.3%)	985 (21.1%)	
65-69	6,262 (13.0%)	626 (13.4%)		655 (14.0%)	626 (13.4%)	
70-74	6,468 (13.5%)	681 (14.6%)		666 (14.3%)	681 (14.6%)	
≥75	14,037 (29.2%)	1,571 (33.7%)		1,558 (33.4%)	1,571 (33.7%)	
CABG or PCI	5,454 (11.3%)	124 (2.7%)	0.346	111 (2.4%)	124 (2.7%)	0.018

Any diuretic	11,396 (23.7%)	1,342 (28.8%)	0.115	1,325 (28.4%)	1,342 (28.8%)	0.008
Ischemic Stroke or TIA	5,727 (11.9%)	730 (15.6%)	0.108	783 (16.8%)	730 (15.6%)	0.031
Calcium channel blockers	5,386 (11.2%)	833 (17.9%)	0.189	825 (17.7%)	833 (17.9%)	0.004
Statin	22,441 (46.7%)	2,104 (45.1%)	0.032	2,073 (44.4%)	2,104 (45.1%)	0.013
Colonoscopy	2,733 (5.7%)	268 (5.7%)	0.002	262 (5.6%)	268 (5.7%)	0.006

Legend: SD - standardized difference (balance indicated if < 0.1), Sdev – standard deviation, TIA - transient ischemic attack, CABG - coronary artery bypass graft, PCI - percutaneous coronary intervention, COPD – chronic obstructive pulmonary disease, NSAIDs – non-steroidal anti-inflammatory drugs



## Methodology for Selecting Telmisartan

We reviewed all supplemental application approvals for previously approved novel therapeutic agents that occurred between 2005 and 2014 from the publically available Drugs@FDA database.<sup>1</sup> The supplemental indications were classified into three mutually exclusive categories: ‘new indication’, ‘modification’ of an already approved indication, and ‘expansion’ in patient population.<sup>1</sup> New indication meant that no similar use was ever previously approved for the medication. An example of ‘modification’ is a diabetes drug being used to treat the same condition (e.g., diabetes mellitus) as its initial approval, but now it can be used in combination with another diabetes medication. Expansion generally referred to a drug being used to treat the same condition (e.g., diabetes mellitus) but in a different age group (e.g., children with diabetes mellitus).

We identified 138 new indications, 86 modifications to the initial indication, and 66 expansions to the initial indication. We focused on new indications since these require a high level of evidence (i.e., randomized clinical trial) before they are granted.

Of the 138 new indications, 108 (78.3%) of the clinical trials supporting the new indications had a primary outcome that was not identifiable in US longitudinal healthcare databases (e.g., pathology results, change in clinical scores, radiologic tumour response), 12 (8.70%) of the trials did not have an active comparator (i.e., placebo-controlled trials), 4 (2.90%) of the trials were based predominantly on in-hospital medication administration (e.g., post-operative nausea medication, anesthetic medications), and 14 (10.14%) of trials were potentially replicable.

Of the 14 potentially replicable trials we selected telmisartan and did not run analyses on the other 13. Of the remaining 13, most (N=8) were related to low molecular weight heparin

medications or direct oral acting anticoagulants where the initial indication was typically venous thromboembolism prophylaxis, for example, and the new indication was the treatment of venous thromboembolism. Of the remaining five, two had laboratory based outcomes (e.g., change in cholesterol or blood glucose) which are not currently identifiable in most US longitudinal healthcare claims databases, one was an anti-rejection medication (i.e., tacrolimus) to prevent graft rejection following heart transplant, one was a medication (i.e., candesartan) for the treatment of heart failure, and one was an anticoagulant (i.e., bivalirudin) used for patients undergoing percutaneous coronary intervention.

#### Reference

1. Wang B, Kesselheim AS. Characteristics of efficacy evidence supporting approval of supplemental indications for prescription drugs in united states, 2005-14: systematic review. *BMJ*. 2015;351:h4679.