Table S1. Medication types and Health Insurance Review and Assessment Service codes.

Medications	Codes
Alpril	104201, 104202
Benazepril	114701
Captopril	122901, 122902, 122903
Cilazapril	133001, 133002, 133003
Enalapril	151601, 151603
Fosinopril	163501, 163502
Imidapril	173401, 173402
Moexipril	196801, 196802
Lisinopril	184501
Perindopril	211301, 211302, 501601, 501602
Quinapril	221901,
Ramipril	222401, 222402, 222404
Zofenopril	510401, 510402, 510403
Temocapril	235002
Delapril	140901, 140902
Captopril + hydrochlorothiazide	262200, 262300
Enalapril + hydrochlorothiazide	440300, 453700, 453600
Ramipril + felodipine	447100, 447200
Ramipril + hydrochlorothiazide	448600, 448700
Perindopril + indapamide	556200
Lisinopril + hydrochlorothiazide	499200, 499300
Moexipril + hydrochlorothiazide	440800, 497900
Enalapril + nitrendipine	466000
Candesartan	122601, 122602, 122603
Irbesartan	177301, 177303
Losartan	185701, 185702
Valsartan	247101, 247102, 247103, 247104

Fimasartan	515201, 515202, 515203
Azilsartan	662401, 662402, 662403
Telmisartan	378801, 378802
Eprosartan	429201
Olmesartan	468501, 468502, 468503, 520901, 520902
Valsartan + amlodipine	492800, 492900, 495800, 522600, 522700, 522800, 522900, 523000, 523100, 523200, 523300, 523400
Valsartan + lercanidipne	522200. 522300. 522400
Valsartan + pitavastatin	634900, 635000, 635100, 635200
Valsartan + sacubitril	651401, 651402, 651403
Valsartan + rosuvastatin	629700, 629800, 525000, 525100, 525200, 525300,
Valsartan + hydrochlorothiazide	356400, 442600
Olmesaetan + amlodipine	500500, 500600, 547500. 547600, 547700, 547800, 547900, 548000, 582200, 582400, 629400, 629500, 629600, 631300, 632800, 632900, 633000
Olmesartan + hydrochlorothiazide	513600
Olmesartan + hydrochlorothiazide + amlodipine	519700, 519800, 519900, 520000, 520100
Olmesartan + rosuvastatin	653200, 644100, 644200, 526300, 526400, 526500, 526900
Telmisartan + hydrochlorothiazide	502600, 443200, 443300
Telmisartan + rosuvastatin	629900, 630000, 630100, 630200, 631600, 631700
Telmisartan + amlodipine	511500, 511600, 511700, 521200, 521300, 521400, 623100, 644800
Telmisartan+ hydrochlorothiazide + amlodipine	663500, 663600, 663700, 663800
Telmisartan + rosuvastatin + amlodipine	671700, 671600, 671500, 671400, 671300, 671200,
Losartan + hydrochlorothiazide	262500, 378900, 486900
Losartan + amlodipine	502700, 503000, 513900, 637400, 637500, 637600
Losartan+ rosuvastatin+ amlodipine	663900, 664000, 664100, 664200, 664300, 664400,
Losartan+chlorthalidone+ amlodipine	662800, 662900, 663000
Fimasartan + hydrochlorothiazide	522000, 526800

Fimasartan + amlodipine	651900, 652000, 652100, 652700, 651900
Fimasartan + rosuvastatin	654600, 654700, 654800, 654900, 655000
Candesartan + hydrochlorothiazide	423700
Candesartan + amlodipine	652900, 653000, 653100, 652900, 652900
Candesartan + rosuvastatin	673700, 661800, 661900, 662000, 662100
Irbesartan + hydrochlorothiazide	385700, 385800
Irbesartan + atorvastatin	527000, 527100, 524000, 524100
Azilsartan + chlorthalidone	673500, 673600
Eprosartan + hydrochlorothiazide	460500
Amlodipine	495901, 459802, 483201, 486501, 107601, 107601, 459801, 459801, 459901, 464601, 470801, 476201, 479701, 483202, 486502, 107602, 107602, 470802
Amlodipine + atorvastatin	614500, 472300, 472400, 472500, 518900
Amlodipine + rosuvastatin	673900, 674000, 674100
Amosulalol	107901, 107902
Arotinolol	110202, 110201
Nolol	483102, 111402, 483101, 111403, 111401
Nolol + chlorthalidone	262100, 460200
Barnidipine	114003, 114001, 114002
Benidipine	115101, 115102, 115104, 115103
Betaxolol	116801, 116803
Bevantolol	117002, 117001
Bisoprolol	117904, 117903, 117902, 117901
Bisoprolol + hydrochlorothiazide	469800, 470000, 469900
Carteolol	124801
Carvedilol	125005, 125003, 662201, 125008, 125001, 662202, 125007, 125002, 125006, 125004
Celiprolol	129101
Cilnidipine	133102, 133101

Clonidine	136505
Diltiazem	145706, 145707, 145707, 145703, 145706, 145707
Doxazocin	149101, 149102, 149104, 149103
Efonidipine	441202, 441201
Felodipine	157503, 157501
Felodipine + metoprolol	262400
Hydralazine	170701
Lacidipine	180301, 180302, 180303
Lercanidipine	182001, 182002
Manidipine	188001, 188002
Metoprolol	194003, 193802, 262400
Metoprolol + hydrochlorothiazide	262600
Metoprolol + felodipine	262400
Minoxidil	196102
Nadolol	198301
Nebivolol	489501, 489502, 489503
Nicardipine	201003, 201002
Nifedipine	201407, 201405, 528201, 201409, 528202, 201401, 201401, 201408
Nimodipine	201901, 356202, 356203, 356201, 356202
Nisoldipine	356202
Propranolol	219901, 219904, 219906, 219905
Terazosin	235501, 235502, 235503, 616501
Verapamil	247606, 247607, 247603, 247605, 247601
Atorvastatin + ezetimibe	633800, 633900, 634800
Pitavastatin + fenofibr	679300
Rosuvastatin + ezetimibe	640700, 640800, 640900

Aspirin	110701, 110702, 110801, 110802, 111001, 111001, 111001, 111002, 111003, 111003
Clopidogrel	133201, 133201, 133201, 133202, 133203, 506100
Cilostazol	136901, 492501, 495201, 498801, 501501
Ticlopidine	498900, 239201, 239202
Aspirin + bethocarbamol	256800
Aspirin + clopidogrel	517900, 517900, 517900, 667500
Aspirin + dipyridamole	489700
Atorvastatin	111502, 502202, 633900, 472400, 518900, 524100, 527000, 672000, 672100, 111503, 502203, 634800, 472500, 111504, 502204
Fluvastatin	162401, 162402, 162403
Lovastatin	185801
Pitavastatin	470901, 470902, 470903
Pravastatin	216601, 216602, 216603, 216604
Rosuvastatin	454001, 454002, 454002, 454003, 454003, 454005
Simvastatin	227801, 227802, 227803, 227805, 227806
Dexlansoprazole	621901, 621902
Esomeprazole	509901, 367202, 498002, 367202, 509902, 518000, 367201, 523500, 498001, 527400, 367201, 670700, 459401
Ilaprazole	505501
Lansoprazole	181301, 181301, 181301, 181302, 181302, 181302, 181302
Omeprazole	204403, 204401, 204401, 664500, 204402, 640200, 204501
Pantoprazole	519202, 519202, 208901, 519201, 208802, 519201, 208902, 208801, 519203, 656701, 208801
Cimetidine	133301, 133302, 133303, 133305, 133301, 133330
Famotidine	157301, 157302, 157303, 157302
Nizatidine	202701, 202704
Ranitidine	222801, 222803, 222805, 222830, 222831, 222802, 222804
Roxatidine	225201, 225202

Ranitidine + sucralfate + tripotassium bismuth	271800, 631800
Lafutidine	489302

Table S2. Proton pump inhibitor prescription and site-specific cancer risk.

	Univariable		Multivariable	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
Stomach cancer				
Ref: No-Prescription				
Short	0.88 (0.71–1.08)	0.203	0.88 (0.71–1.08)	0.213
Long	0.98 (0.83–1.15)	0.788	0.88 (0.75–1.04)	0.132
Ref: Short				
Long	1.12 (0.89–1.41)	0.341	1.00 (0.80–1.27)	0.969
Colorectal cancer				
Ref: No-Prescription				
Short	1.06 (0.90–1.25)	0.465	1.07 (0.91–1.26)	0.436
Long	1.01 (0.88–1.16)	0.899	0.94 (0.82–1.08)	0.372
Ref: Short				
Long	0.95 (0.79–1.14)	0.579	0.88 (0.73–1.06)	0.171
Pancreatic cancer				
Ref: No-Prescription				
Short	1.00 (0.76–1.30)	0.978	0.90 (0.69–1.18)	0.450
Long	1.63 (1.36–1.97)	<0.001	1.35 (1.11–1.64)	0.003
Ref: Short				
Long	1.64 (1.24–2.17)	<0.001	1.49 (1.13–1.98)	0.005
Bladder cancer				
Ref: No-Prescription				
Short	1.12 (0.85–1.48)	0.409	1.13 (0.86–1.49)	0.388
Long	1.10 (0.87–1.38)	0.433	0.99 (0.78–1.26)	0.951
Ref: Short				
Long	0.98 (0.72–1.33)	0.873	0.88 (0.64–1.20)	0.410
Thyroid cancer				
Ref: No-Prescription				
Short	1.39 (1.14–1.70)	0.001	1.34 (1.09–1.64)	0.005
Long	1.24 (1.05–1.48)	0.014	1.35 (1.12–1.61)	0.001
Ref: Short				
Long	0.90 (0.72–1.12)	0.333	1.01 (0.80–1.26)	0.946
Lung cancer				
Ref: No-Prescription				
Short	1.10 (0.92–1.31)	0.291	1.09 (0.91–1.30)	0.347
Long	1.16 (1.01–1.34)	0.034	1.04 (0.90–1.21)	0.570
Ref: Short				
Long	1.10 (0.87–1.28)	0.556	0.96 (0.79–1.16)	0.667
Breast cancer				
Ref: No-Prescription				
Short	0.98 (0.74–1.29)	0.865	1.01 (0.76–1.34)	0.943
Long	1.03 (0.82–1.30)	0.775	1.15 (0.91–1.46)	0.236
Ref: Short				
Long	1.06 (0.78–1.44)	0.716	1.14 (0.84–1.56)	0.403
Prostate cancer				
Ref: No-Prescription				
Short	1.51 (1.23–1.85)	<0.001	1.40 (1.14–1.73)	0.001
Long	1.20 (0.99–1.44)	0.053	1.03 (0.86–1.25)	0.737
Ref: Short				
Long	0.80 (0.63–1.00)	0.054	0.74 (0.58–0.93)	0.011
Liver cancer				
Ref: No-Prescription				
Short	1.25 (1.07–1.48)	0.006	1.20 (1.02–1.42)	0.026

Long	1.36 (1.19–1.54)	<0.001	1.22 (1.06–1.40)	0.004
Ref: Short				
Long	1.08 (0.91–1.29)	0.387	1.01 (0.85–1.21)	0.895
Gallbladder and biliary duct cancer				
Ref: No-Prescription				
Short	1.16 (0.82–1.62)	0.407	1.13 (0.80–1.59)	0.497
Long	1.12 (0.84–1.48)	0.435	1.04 (0.78–1.40)	0.775
Ref: Short				
Long	0.97 (0.66–1.41)	0.870	0.93 (0.63–1.36)	0.695
Renal cancer				
Ref: No-Prescription				
Short	0.95 (0.80–1.13)	0.554	0.98 (0.83–1.17)	0.857
Long	1.11 (0.98–1.27)	0.106	1.21 (1.06–1.39)	0.006
Ref: Short				
Long	1.17 (0.97–1.41)	0.095	1.23 (1.02–1.48)	0.031
Uterus or cervical cancer				
Ref: No-Prescription				
Short	1.24 (0.88–1.74)	0.222	1.07 (0.75–1.51)	0.722
Long	0.87 (0.64–1.20)	0.411	0.84 (0.60–1.17)	0.293
Ref: Short				
Long	0.71 (0.47–1.06)	0.093	0.77 (0.52–1.18)	0.248

Multivariable models adjusted for age, sex, vascular access type, hemodialysis vintage, underlying cause of end-stage kidney disease; Charlson Comorbidity Index score; Kt/V_{urea}; ultrafiltration volume; hemoglobin; serum albumin, creatinine, phosphorus, and calcium; use of renin-angiotensin system blockers, statins, clopidogrel, aspirin, or H_2-receptor blockers; and presence of myocardial infarction or congestive heart failure; models were fitted using the enter method.

Abbreviations: HR, hazard ratio; CI, confidence interval; No-Prescription, patients without proton pump inhibitor prescription for 1 year; Short, patients with prescription for < 60 days in 1 year; Long, patients with prescription for ≥ 60 days in 1 year.

Table S3. Cancer types among patients diagnosed with cancer

	Total (n = 62,951)	No-Prescription (n = 37,934)	Short (n = 9,909)	Long (n = 18,108)
Thyroid	688 (1.0%)	369 (1.0%)	127 (1.3%)	192 (1.1%)
Lung	1039 (1.6%)	584 (1.5%)	161 (1.6%)	294 (1.6%)
Colorectum	1183 (1.8%)	695 (1.8%)	185 (1.9%)	303 (1.7%)
Stomach	829 (1.3%)	504 (1.3%)	111 (1.1%)	214 (1.2%)
Breast	427 (0.6%)	243 (0.6%)	67 (0.7%)	117 (0.6%)
Prostate	648 (1.0%)	356 (0.9%)	121 (1.2%)	171 (0.9%)
Liver	1160 (1.8%)	610 (1.6%)	192 (1.9%)	358 (2.0%)
Pancreas	524 (0.8%)	270 (0.7%)	67 (0.7%)	187 (1.0%)
Gall bladder or bile duct	263 (0.4%)	148 (0.4%)	43 (0.4%)	72 (0.4%)
Kidney	1199 (1.8%)	703 (1.9%)	166 (1.7%)	330 (1.8%)
Uterus or cervix	234 (0.4%)	139 (0.4%)	43 (0.4%)	52 (0.3%)
Bladder	405 (0.6%)	230 (0.6%)	65 (0.7%)	110 (0.6%)

Proportions were calculated using each group total as the denominator. Some patients were diagnosed with more than one primary cancer during follow-up.

Abbreviations: No-Prescription, patients without a proton pump inhibitor prescription within 1 year; Short, patients with a prescription for < 60 days within 1 year; Long, patients with a prescription for ≥ 60 days within 1 year.

Table S4. Prescription of proton pump inhibitors and any-cancer risk, stratified by immunosuppressive agent use

	Univariable		Multivariable	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
ISA (+)				
Any-cancer				
Ref: No-Prescription				
Short	1.04 (0.91–1.20)	0.547	1.01 (0.88–1.17)	0.867
Long	1.15 (1.02–1.29)	0.019	1.07 (0.95–1.21)	0.257
Ref: Short				
Long	1.10 (0.94–1.28)	0.221	1.06 (0.91–1.23)	0.465
Mortality				
Ref: No-Prescription				
Short	1.01 (0.83–1.22)	0.920	1.02 (0.84–1.24)	0.865
Long	0.96 (0.82–1.12)	0.588	0.95 (0.81–1.12)	0.541
Ref: Short				
Long	0.95 (0.77–1.17)	0.613	0.93 (0.76–1.15)	0.527
ISA (-)				
Any-cancer				
Ref: No-Prescription				
Short	1.11 (1.03–1.20)	0.006	1.10 (1.02–1.18)	0.014
Long	1.11 (1.04–1.18)	0.001	1.05 (0.99–1.12)	0.127
Ref: Short				
Long	1.00 (0.92–1.08)	0.939	0.96 (0.88–1.04)	0.296
Mortality				
Ref: No-Prescription				
Short	0.89 (0.80–0.99)	0.032	0.91 (0.82–1.02)	0.094
Long	1.01 (0.93–1.09)	0.824	0.92 (0.84–0.99)	0.040
Ref: Short				
Long	1.13 (1.01–1.27)	0.037	1.00 (0.89–1.13)	0.967

Multivariable models were adjusted for age, sex, vascular access type, hemodialysis vintage, underlying cause of end-stage kidney disease, Charlson Comorbidity Index score, Kt/V_{urea}; ultrafiltration volume, hemoglobin, serum albumin, creatinine, phosphorus, and calcium, use of renin-angiotensin system blockers, statins, clopidogrel, aspirin, or H_2-receptor blockers, and presence of myocardial infarction or congestive heart failure. Models were fitted using the enter method.

Abbreviations: HR, hazard ratio; CI, confidence interval; ISA, immunosuppressive agents; No-Prescription, patients without a proton pump inhibitor prestcription within 1 year; Short, patients with a prescription for < 60 days within 1 year; Long, patients with a prescription for ≥ 60 days within 1 year.

Table S5. Baseline characteristics after weighting

	No-Prescription (*n* = 65,446)	Short group (*n* = 64,085)	Long group (*n* = 64,043)	*P*-value
Age (years)	60.7 ± 0.1	60.6 ± 0.1	60.8 ± 0.1	0.566
Male sex	39,465 (60.3%)	38,019 (59.3%)	37,980 (59.3%)	0.133
Body mass index (kg/m^2)	22.7 ± 0.0	22.7 ± 0.0	22.7 ± 0.0	0.258
Hemodialysis vintage (months)	52 ± 0	52 ± 1	52 ± 0	0.981
Diabetes as underlying cause of ESKD	30,184 (46.1%)	28,964 (45.2%)	29,076 (45.4%)	0.238
CCI score	7.4 ± 0.0	7.5 ± 0.0	7.5 ± 0.0	0.012
Arteriovenous fistula	55,883 (85.4%)	54,443 (85.0%)	54,661 (85.4%)	0.476
Kt/V_{urea}	1.52 ± 0.00	1.52 ± 0.00	1.52 ± 0.00	0.795
Ultrafiltration volume (L/session)	2.30 ± 0.00	2.29 ± 0.01	2.29 ± 0.01	0.697
Hemoglobin (g/dL)	10.7 ± 0.0	10.7 ± 0.0	10.7 ± 0.0	0.698
Serum albumin (g/dL)	4.0 ± 0.0	4.0 ± 0.0	4.0 ± 0.0	0.425
Serum phosphorus (mg/dL)	4.97 ± 0.01	4.97 ± 0.01	4.94 ± 0.01	0.737
Serum calcium (mg/dL)	8.87 ± 0.00	8.87 ± 0.01	8.86 ± 0.01	0.488
Serum creatinine (mg/dL)	9.45 ± 0.01	9.44 ± 0.03	9.46 ± 0.02	0.767
RASB use	42,567 (65.0%)	42,508 (66.3%)	42,556 (66.4%)	0.023
Aspirin use	16,821 (25.7%)	16,718 (26.1%)	17,082 (26.7%)	0.146
Clopidogrel use	9,759 (14.9%)	9,553 (14.9%)	10,145 (15.8%)	0.031
Statin use	29,864 (45.6%)	29,934 (46.7%)	30,130 (47.0%)	0.041
H_2 receptor-blocker use	22,060 (33.7%)	22,169 (34.6%)	22,487 (35.1%)	0.034
MI or CHF	30,744 (47.0%)	29,748 (46.4%)	30,263 (47.3%)	0.333

Data are presented as means ± standard errors for continuous variables and numbers (percentages) for categorical variables. *P*–values were calculated using a general linear model with a complex survey design that included sample weights.

Abbreviations: CCI, Charlson Comorbidity Index; CHF, congestive heart failure; ESKD, end-stage kidney disease; MI, myocardial infarction; RASB, renin–angiotensin system blocker; No-Prescription, patients without a proton pump inhibitor prescription within 1 year; Short, patients with a prescription for < 60 days within 1 year; Long, patients with a prescription for ≥ 60 days within 1 year.

Table S6. Proton pump inhibitor prescription and any cancer or mortality in the weighted cohort.

Outcome and exposure	Univariable		Multivariable	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Any-cancer				
Ref: No-Prescription				
Short	1.08 (1.04–1.11)	<0.001	1.07 (1.04–1.11)	<0.001
Long	1.09 (1.05–1.12)	<0.001	1.08 (1.05–1.12)	<0.001
Ref: Short				
Long	1.01 (0.98–1.04)	0.528	1.01 (0.98–1.04)	0.576
Mortality				
Ref: No-Prescription				
Short	0.93 (0.89–0.97)	0.001	0.95 (0.91–0.99)	0.034
Long	0.87 (0.83–0.91)	<0.001	0.90 (0.86–0.94)	<0.001
Ref: Short				
Long	0.93 (0.89–0.98)	0.002	0.95 (0.91–0.99)	0.018

Multivariable models were adjusted for age, sex, vascular access type, hemodialysis vintage, underlying cause of end-stage kidney disease, Charlson Comorbidity Index score, Kt/V_{urea}, ultrafiltration volume, hemoglobin, and serum albumin, creatinine, phosphorus, and calcium; use of a renin–angiotensin system blocker, statins, clopidogrel, aspirin, or H_2-receptor blockers; and presence of myocardial infarction or congestive heart failure. Models were fitted using the enter method.

Abbreviations: HR, hazard ratio; CI, confidence interval; No-Prescription, patients without a proton pump inhibitor prescription within 1 year; Short, patients with a prescription for < 60 days within 1 year; Long, patients with a prescription for ≥ 60 days within 1 year.

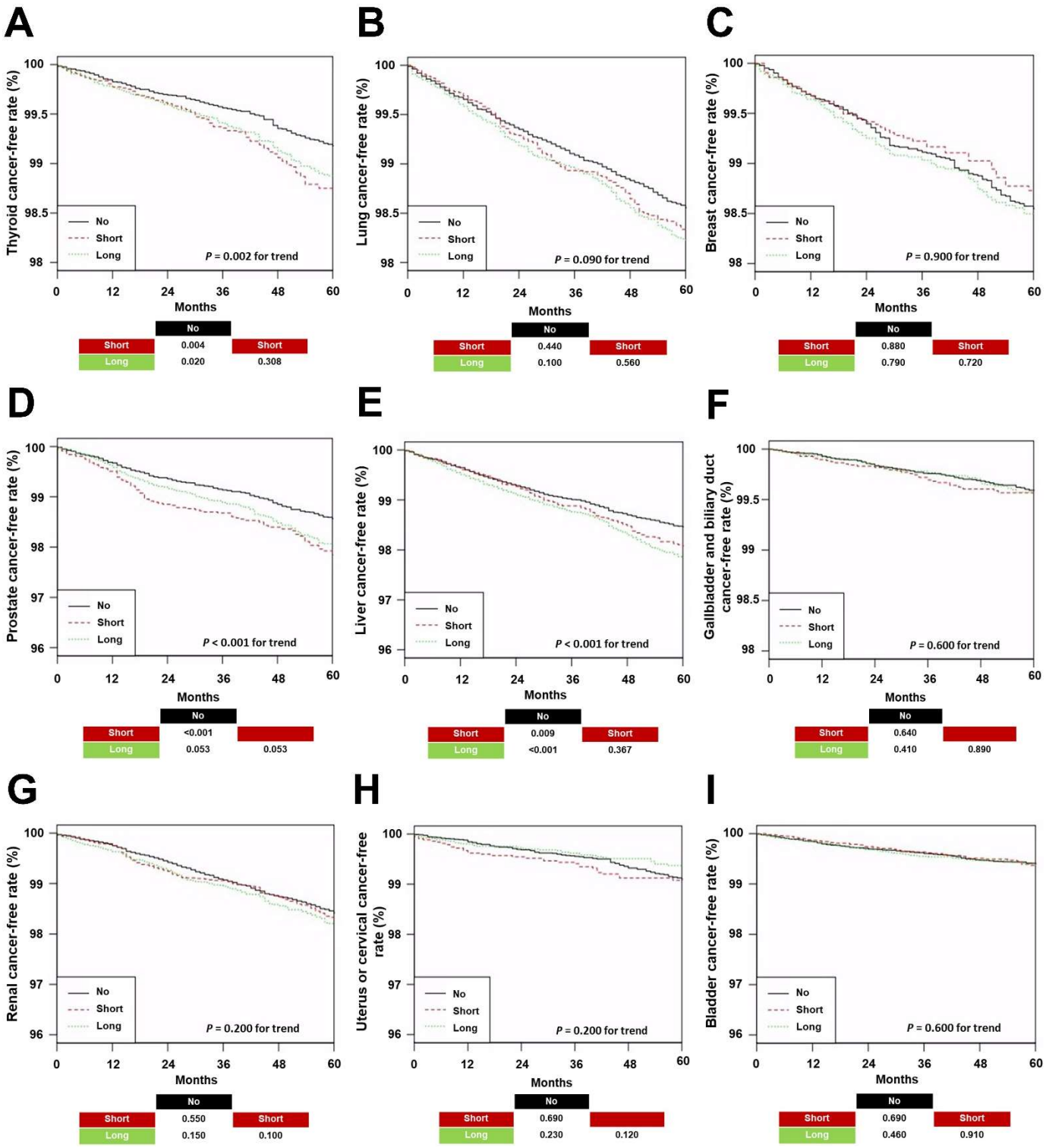


Figure S1. Kaplan–Meier curves of cancer-free rates by proton pump inhibitor use. Cancer-free rates for (A) thyroid, (B) lung, (C) breast, (D) prostate, (E) liver, (F) gallbladder and biliary duct, (G) renal, (H) uterine or cervical, and (I) bladder cancer.

P-values for pairwise comparisons with log-rank tests were presented at the bottom of the graph.

Abbreviations: No, patients without proton pump inhibitor prescription for 1 year; Short, patients with prescription for < 60 days in 1 year; Long, patients with prescription for ≥ 60 days in 1 year.

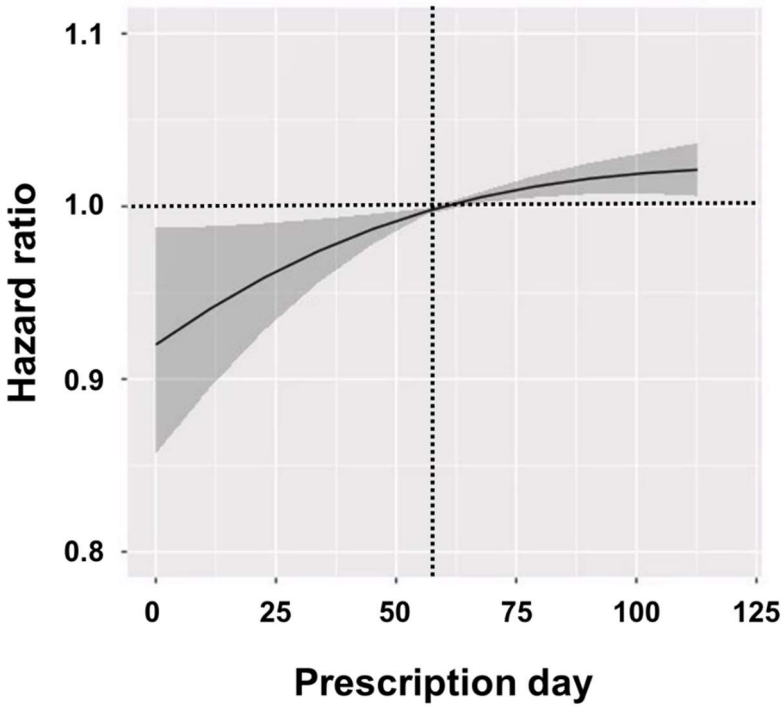


Figure S2. Spline curve plotting hazard ratio and 95% confidence interval for cancer incidence according to prescription days of proton pump inhibitors. The reference point was established at 60 prescription days.

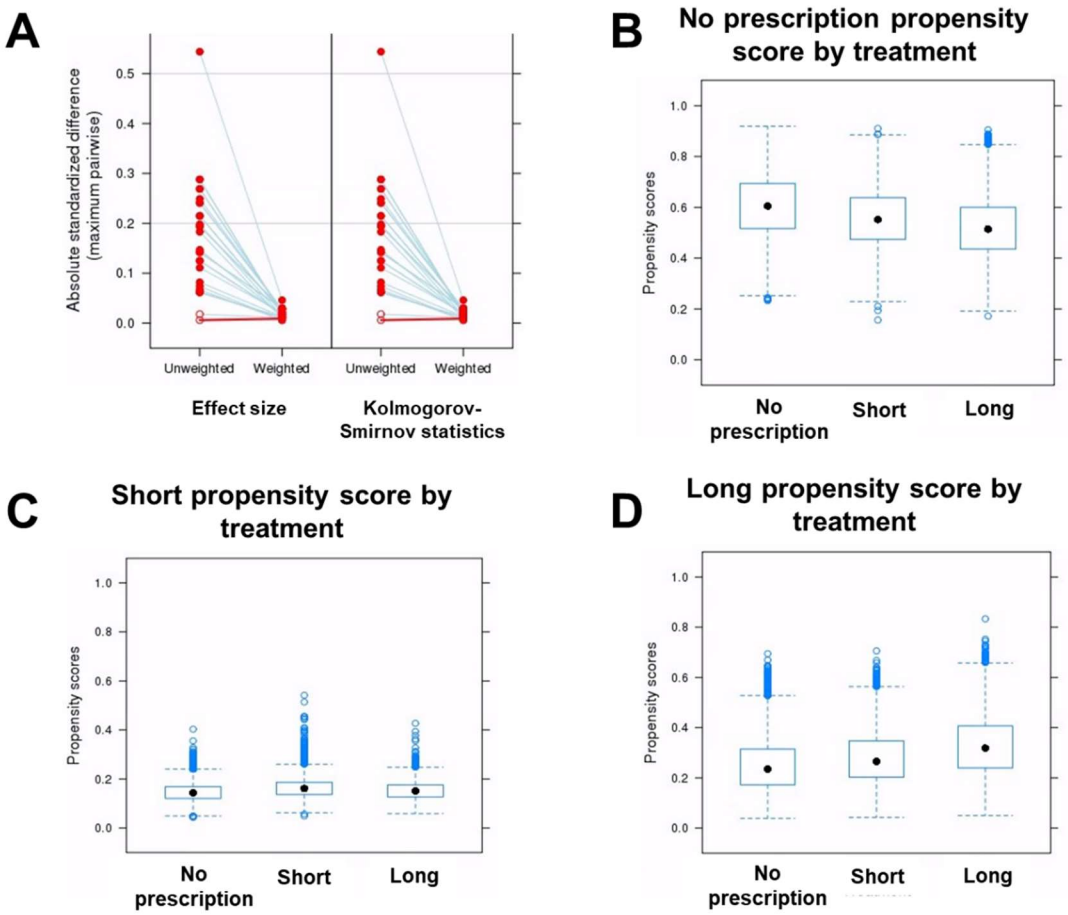


Figure S3. Balance test. (A) Absolute standardized difference plots for estimating propensity scores used to generate weights. (B-D) Boxplots illustrating the spread of propensity scores by treatment group. The filled black circles indicate the median propensity score in each treatment group. As shown, propensity score distributions overlapped substantially.

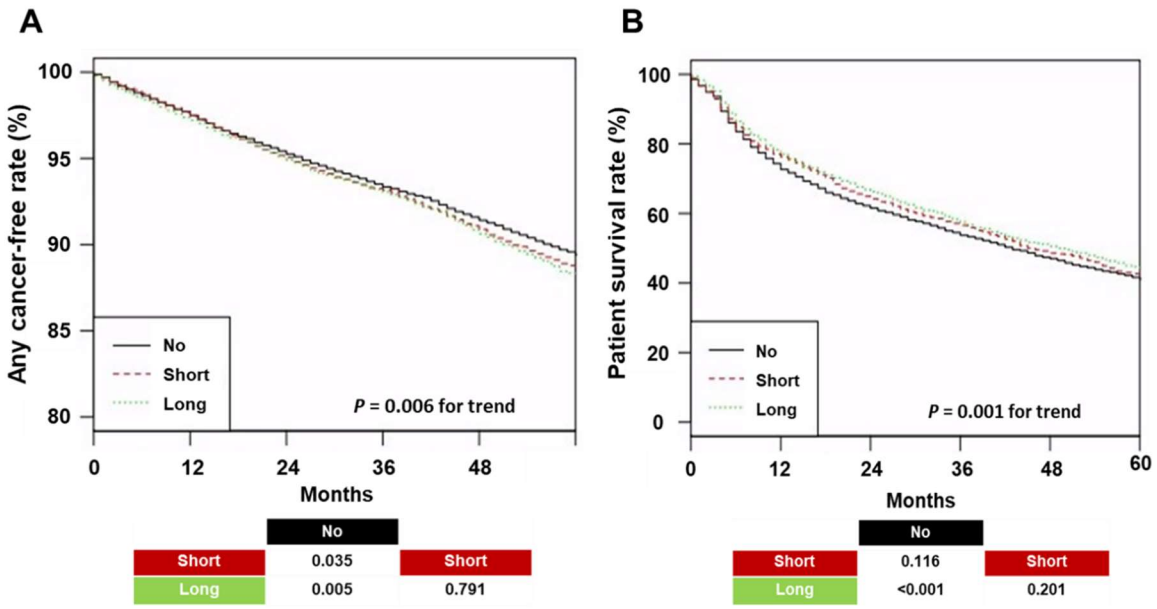


Figure S4. Kaplan–Meier curves for any cancer-free survival and overall survival by proton pump inhibitor use. (A) Any cancer-free survival in the weighted cohort; (B) overall survival among patients with cancer. Pairwise log-rank *P*-values are shown at the bottom of the graph. The cancer-free rates were 89.4%, 88.7%, and 88.2% in the No-Prescription, Short, and Long groups, respectively (Figure A). The survival rates among patients with cancer were 41.2%, 42.2%, and 44.3% in the No-Prescription, Short, and Long groups, respectively (Figure B).

Abbreviations: No, patients without a prescription for a proton pump inhibitor use in a given year; Short, patients with prescriptions for < 60 days in a given year; Long, patients with prescriptions for ≥ 60 days in a given year.