Outcomes with Concurrent Use of Clopidogrel and Proton-Pump Inhibitors: On-Line Appendix

This on-line appendix provides supplementary tabular and graphic material. It includes both more in-depth information for the cohort assembly and statistical analysis as well as more details for study results. It should only be read in conjunction with the primary manuscript, which describes the study methods and presents the main findings.

Cohort Assembly

Figure A-1 shows the study flow diagram, indicating how the clopidogrel users included in the study analysis were identified. During the study period, there were 26,315 potentially eligible clopidogrel users. Of these, 4859 (18%) were ineligible, primarily because of a prior exclusion illness. Of the remaining, 860 had no qualifying study follow-up (PPI use other than current use or nonuse).

Statistical Analysis: Propensity Score

The primary method used to control for confounding by baseline cohort characteristics is the propensity score, defined as the baseline probability of proton-pump inhibitor (PPI) use, given a particular pattern of baseline covariates. Inclusion of the propensity score in regression models relating PPI use to study endpoints can control for confounding by the covariates included in the propensity score. Given that the true propensity score is unknown and the analysis uses an estimated propensity score, several checks are appropriate.

The propensity score was estimated using a logistic regression model, where the dependent variable was 1 for baseline PPI users and 0 for nonusers. The model was simple logit-linear, with a linear term for each covariate. *Table A-1* shows the baseline covariates considered and the odds ratios associated with each. Some of the key covariates that indicated high likelihood of baseline PPI use were calendar year (probably reflecting a secular trend of increasing PPI use), indicators of baseline upper gastrointestinal disease (the indication for PPIs), and indicators of frequent use of medical care (either prescriptions for medications for symptoms, such as benzodiazepines or outpatient physician visits).

One test of the adequacy of the model used to estimate the propensity score is whether or not there is balance in the constituent covariates between the user and nonuser groups after controlling for the propensity score. In this study, Table 1 (primary manuscript) shows the p-values comparing the two groups after controlling for propensity score, all of these are far removed from statistical significance, indicating good balance.

Another important assumption for propensity score methods is that every cohort member has a non-zero probability of being either a PPI user or nonuser. If there are cohort members who must always receive a PPI or those who could never receive a PPI, they would be excluded, because the relevant comparison is between persons who are eligible to receive a PPI but who may or may not actually get one. We test this assumption by reviewing the overlap in the distribution of the propensity score in PPI users and nonusers. Although, as expected and as in shown in *Figure A-2*, this distribution differed for users and non-users, there was nearly complete overlap. For users and nonusers, the respective ranges of the propensity score were [.036,.997], and [.029,.983].

The study analysis controls for baseline covariates by including the propensity score deciles in the regression models. The resulting incidence rate-ratio (IRR, the study measure of effect) for PPI use is a weighted average of the within-decile IRRs. Thus it is appropriate to examine the within-decile IRRs to determine if there is interaction with the propensity score; *Table A-2* suggests there is little evidence for material interaction for either the gastroduodenal bleeding hospitalization or serious cardiovascular disease endpoints.

Another check was comparison of a model with all of the covariates to one with the propensity score deciles. This model was run for the serious cardiovascular disease endpoint, given that the expected effect of a PPI was small and thus this analysis would be most sensitive to errors in the underlying assumptions. The IRR estimates from the two models were identical, to two decimal places.

Statistical Analysis: Hospital Exchangeability Assumption

The cohort is formed of persons who have a qualifying hospital stay during which they are treated for cardiovascular disease. Let the hospital from which a patient was discharged just prior to t_0 be denoted as the *qualifying hospital*. Thus, it is possible that the cohort actually consists of "clusters" of patients, each consisting of patients discharged from the same qualifying hospital at t_0. If so, patients within a cluster might be more similar with respect to likelihood of an endpoint that are patients in different clusters. This is the basis for our primary analysis using a robust variance estimator that allows for within-hospital correlation.

However, for the gastroduodenal bleeding hospitalization endpoint, there are many qualifying hospitals for which there are no endpoints for either the PPI user or nonuser groups. If there is a strong clustering effect, then the analysis requires a strong exchangeability assumption, that is, that patients from one small qualifying hospital are similar to patients from another small qualifying hospital.

Table A-3 provides information on the number of such small qualifying hospitals. The cohort is classified into tertiles according to the size of the qualifying hospital. In the top tertile, the exchangeability assumption is not an issue, every qualifying hospital has gastroduodenal endpoints for both PPI users and nonusers. Of the 9 hospitals in the middle tertile, 2 had no endpoints for the PPI user group and of the 119 in the lower tertile, 103 (86.6%) have no endpoints for the PPI user group.

However, there are two lines of evidence that suggest findings are robust. First is the clinical plausibility of a strong clustering effect. The median length of stay for the qualifying hospitalization is 3 days. The gastroduodenal endpoints occur a median of 328 days following the qualifying hospital discharge. The patients are seen during the qualifying hospitalization for coronary artery disease. Thus, for example, a major effect of hospital factors related to a 3 day hospital stay with stenting for angina on a bleed that occurs 11 months later seems unlikely.

Second, analysis by tertiles according to qualifying hospital cohort patient volume shows no evidence of variation by this factor (Table A-3).

Statistical Analysis: Time-Dependent Covariates, Model Fitting Results

The propensity scores included in all models were constructed from the value of study variables at t_0 and thus wouldn't account for changes in these factors. For this reason, all models included additional time-dependent covariates, using traditional regression methods. This raises the possibility of introduction of multicolinearity and adjustment for factors on the causal pathway. The robustness of the analysis to violations of these assumptions is explored in alternative analyses that exclude time-dependent covariates.

Table A-4 presents the primary regression model for the gastroduodenal bleeding hospitalization endpoint. As expected, the baseline propensity score is a good predictor for this endpoint, given that the factors associated with PPI use should identify patients at higher risk of subsequent upper gastrointestinal bleeding. With regard to the time-dependent covariates, important variables are medications known to increase the risk of bleeding, such as oral anticoagulants, NSAIDs, and low-dose aspirin, as well as indicators of general medical comorbidity.

Table A-5 presents the primary regression model for the serious cardiovascular disease endpoint. In contrast to the model for the bleeding endpoint, baseline propensity score is not a good predictor of future

cardiovascular endpoints. This is evidence that there is not a strong overlap between risk factors for upper gastrointestinal disease and those for cardiovascular disease. In contrast, the type of qualifying hospitalization is a strong predictor, with the greatest risk being for patients who had an acute myocardial infarction, but no revascularization procedures. The time-dependent covariates for new drugs and new diagnoses were chosen as those that were good predictors of baseline prognosis (statistical significance [$p<.01$] in a proportional hazards regression that included all of the variables in the Appendix with a baseline hazard ratio>1.10 or <0.90).

Study Results: Further Details

Figure A-3 presents the risk of gastroduodenal bleeding hospitalizations according to number of risk factors for such bleeding, demonstrating that the absolute risk increases with the number of such factors and that the absolute benefit associated with current PPI use is greatest for high-risk patients.

Table A-6 and *Figure A-4* present further information for the serious cardiovascular disease endpoint for patients whose qualifying hospital stay included percutaneous coronary intervention with stenting. This group is of particular interest because of the importance of antiplatelet therapy to prevent stent occlusion. There was no increased risk of serious cardiovascular disease associated with current PPI use (Table A-4). For the year following stent implantation, the period during which clopidogrel use is thought to be most important to prevent thrombotic events, the cumulative incidence of serious cardiovascular disease was virtually identical for current PPI users and nonusers.

Tables A-7 and *A-8* include sensitivity analyses that assesses the effects of several study assumptions, including the use of time-dependent covariates. They suggest study findings are robust. Similarly, findings are not materially altered if study definitions are modified to make our study more comparable to another recent study.

Table A-1. Variables used to calculate propensity score. Shown are the odds ratio from the logistic regression model, the 95% confidence interval, and the p-value.

	Parameter	Odds Ratio	95% confidence interval		P-value
1	Intercept	0.25533	0.15168	0.42979	<.0001
2	Age, one year increase	1.00114	0.99757	1.00471	0.5328
3	Sex, male vs female	0.96304	0.89765	1.03319	0.2938
4	Calendar year, 1999	0.2885	0.24324	0.34217	<.0001
5	Calendar year, 2000	0.34714	0.29536	0.408	<.0001
6	Calendar year, 2001	0.58054	0.50004	0.674	<.0001
7	Calendar year, 2002	0.77958	0.67621	0.89874	0.0006
8	Calendar year, 2003	1.03826	0.90925	1.18559	0.5791
9	Calendar year, 2004	1.08946	0.96462	1.23046	0.1676
10	Race, White vs not White	1.04624	0.96343	1.13616	0.2826
11	Medicaid enrollment, uninsured vs other	0.93019	0.86352	1.00201	0.0565
12	Qualifying hosp stay, no AMI, no revasc	1.06133	0.83785	1.34441	0.6217
13	Qualifying hosp stay, no AMI, Stent NDE	0.8175	0.65155	1.02573	0.0818
14	Qualifying hosp stay, no AMI, Stent DE	0.86628	0.68061	1.10259	0.2434
15	Qualifying hosp stay, no AMI, CABG	0.98119	0.77957	1.23496	0.8715
16	Qualifying hosp stay, AMI, no PCI	1.04405	0.82544	1.32054	0.7192
17	Qualifying hosp stay, AMI+Stent NDE	0.87511	0.69385	1.10374	0.26
18	Qualifying hosp stay, AMI+Stent DE	0.92056	0.70356	1.20448	0.5462
19	Prior esophageal disease hospitalization	4.18552	3.8206	4.5853	<.0001
20	GI bleeding complication	1.35168	1.01596	1.79833	0.0386
21	Other bleeding complication	0.90205	0.72556	1.12147	0.3534
22	Peptic ulcer hospitalization	2.15537	1.69805	2.73587	<.0001
23	Gastritis	2.03045	1.60513	2.56846	<.0001
24	Other upper GI disease, inpatient	1.65845	1.27184	2.16259	0.0002
25	Prior lower gastrointestinal hospitalization	1.07647	0.92757	1.24928	0.332
26	Prior GI symptoms hospitalization	1.17923	1.05875	1.31342	0.0027
27	Helicobacter pylori eradication treatment	4.04315	2.97682	5.49144	<.0001
28	Any prior histamine2 receptor antagonist	0.80752	0.7512	0.86806	<.0001
29	Sucralfate	3.10307	2.2801	4.22308	<.0001
30	Misoprostol	1.53222	1.09375	2.14647	0.0131
31	Antacid	1.25678	1.03982	1.51901	0.0181
32	Prior NSAID	0.93418	0.85085	1.02567	0.1532
33	Prior coxib	1.48148	1.36705	1.6055	<.0001
34	Systemic corticosteroid	1.19743	1.10921	1.29266	<.0001
35	Dipyridamole	1.11042	0.88801	1.38852	0.3584
36	Diagnosed obesity	0.89836	0.81122	0.99486	0.0395
37	Diagnosed history tobacco use	0.88244	0.81999	0.94963	0.0008
38	ACE inhibitor	0.95619	0.89044	1.02679	0.2177
39	Angiotensin receptor blocker	1.05583	0.95657	1.16538	0.2808
40	Anticoagulant	0.95913	0.86208	1.06711	0.4433
41	Anti-arrhythmic	0.98396	0.87191	1.11041	0.7932
42	Low dose aspirin	1.12208	1.02813	1.2246	0.0098
43	Beta-blocker	1.02922	0.9582	1.10551	0.4298
44	Calcium-channel blocker	1.00619	0.93867	1.07856	0.8618
45	Digoxin	0.93709	0.84147	1.04358	0.2368
46	Loop diuretic	1.04478	0.96501	1.13115	0.2797
47	Other diuretic	1.09363	1.01706	1.17597	0.0157
48	Insulin	1.11936	1.00773	1.24335	0.0354
49	Oral hypoglycemic	1.08788	0.97318	1.21611	0.1384
50	Statin	1.08113	1.00102	1.16766	0.0471
51	Fibrate	1.2107	1.11128	1.31901	<.0001
52	Nitrate	1.10612	1.02773	1.19049	0.0072
53	Other antihypertensive	0.96081	0.87163	1.05912	0.4212
54	Vasodilator	0.99613	0.80728	1.22916	0.9712

55	Other platelet inhibitor	0.78915	0.72837	0.855	<.0001
56	Angina before qual hosp	1.01375	0.93465	1.09954	0.7419
57	Valve disorder before qual hosp	0.90069	0.79983	1.01426	0.0843
58	Conduction disorder before qual hosp	0.89837	0.73001	1.10555	0.3114
59	Arrhythmia before qual hosp	1.07872	0.97268	1.19632	0.1512
60	Pacemaker before qual hosp	1.21561	0.84749	1.74363	0.2888
61	Heart failure before qual hosp	0.99085	0.89336	1.09898	0.8619
62	Stroke before qual hosp	0.89912	0.81055	0.99737	0.0445
63	Cerebrovascular disease before qual hosp	0.96727	0.81077	1.15398	0.7117
64	Peripheral vascular disease before qual hosp	1.05806	0.94492	1.18475	0.328
65	Diabetes before qual hosp	0.96238	0.8513	1.08795	0.54
66	Hypertension before qual hosp	1.03293	0.94631	1.12747	0.4685
67	Lipid disorder before qual hosp	1.05212	0.9752	1.1351	0.1896
68	Renal disorder before qual hosp	0.94974	0.7988	1.1292	0.5593
69	Other cardiovascular disease before qual hosp	1.03858	0.9575	1.12654	0.3614
70	Cardiovascular symptoms before qual hosp	1.22794	1.13862	1.32427	<.0001
71	Angina during qual hosp	1.07511	0.99487	1.16184	0.0673
72	Valve disorder during qual hosp	1.0227	0.9109	1.14822	0.7039
73	Conduction disorder during qual hosp	1.02128	0.86997	1.1989	0.7969
74	Arrhythmia during qual hosp	0.88219	0.80575	0.96589	0.0067
75	Pacemaker during qual hosp	1.08362	0.82253	1.42759	0.568
76	Heart failure during qual hosp	0.96883	0.87765	1.06948	0.53
77	Stroke during qual hosp	0.82699	0.71259	0.95976	0.0124
78	Cerebrovascular disease during qual hosp	0.93737	0.74515	1.17919	0.5807
79	Peripheral vascular disease during qual hosp	0.89012	0.78485	1.00951	0.0699
80	Diabetes during qual hosp	0.84786	0.75847	0.94779	0.0037
81	Hypertension during qual hosp	0.99961	0.92601	1.07907	0.9921
82	Lipid disorder during qual hosp	0.87485	0.81371	0.94058	0.0003
83	Renal disorder during qual hosp	1.28125	1.0731	1.52977	0.0061
84	Other cardiovascular disease during qual hosp	1.02232	0.92052	1.13539	0.6799
85	Cardiovascular symptoms during qual hosp	1.03001	0.95931	1.10592	0.4151
86	Prior fall related injury	0.92805	0.82214	1.04761	0.2272
87	Prior impairment of mobility	1.1766	0.92375	1.49867	0.1877
88	Prior use home oxygen	0.88413	0.70006	1.11659	0.3011
89	Prior neurologic disease	0.92626	0.71364	1.20221	0.5648
90	Prior mental illness	0.87355	0.79698	0.95748	0.0039
91	Prior COPD	0.98729	0.9102	1.07091	0.7578
92	Prior antidepressant	1.25477	1.16743	1.34865	<.0001
93	Prior benzodiazepine/GABA agonist	1.32415	1.23379	1.42113	<.0001
94	Prior antipsychotic	0.92795	0.8125	1.0598	0.27
95	Prior ADHD medication	0.9821	0.67753	1.42358	0.924
96	Prior anticonvulsant	1.08156	0.98585	1.18656	0.0972
97	Prior narcotic analgesic	1.15109	1.06221	1.24741	0.0006
98	Prior musculoskeletal relaxant	1.084	1.00191	1.17282	0.0447
99	Prior antimicrobial	1.17431	1.07873	1.27836	0.0002
100	Prior bronchodilator	1.28536	1.1897	1.38871	<.0001
101	Indicator, prior CV hosp: 0	1.10015	0.93107	1.29994	0.2622
102	Indicator, prior CV hosp: 1	1.10998	0.95989	1.28355	0.1592
103	Indicator, prior CV ER: 0	0.97708	0.86534	1.10324	0.7082
104	Indicator, prior CV ER: 1	0.98323	0.87575	1.1039	0.7746
105	Indicator, prior CV outpatient visits: 0	1.03518	0.88921	1.20511	0.6557
106	Indicator, prior CV outpatient visits: 1	1.05889	0.91844	1.2208	0.4306
107	Indicator, prior CV outpatient visits: 2	1.08901	0.9472	1.25207	0.231
108	Indicator, prior CV outpatient visits: 3-4	1.07149	0.94731	1.21196	0.2719
109	Indicator, prior CV outpatient visits: 5-7	1.13547	1.00507	1.28279	0.0412
110	Indicator, prior non-CV ER: 0	0.93475	0.83868	1.04183	0.2227
111	Indicator, prior non-CV ER: 1	0.91548	0.81458	1.02886	0.1382
112	Indicator, prior non-CV hosp: 0	1.34805	1.0483	1.73351	0.0199
113	Indicator, prior non-CV hosp: 1	1.32725	1.00975	1.74459	0.0424
114	Indicator, prior non-CV outpatient visits: 0	0.64105	0.53549	0.76743	<.0001
115	Indicator, prior non-CV outpatient visits: 1	0.4902	0.40668	0.59088	<.0001
116	Indicator, prior non-CV outpatient visits: 2	0.56954	0.47533	0.68242	<.0001

117	Indicator, prior non-CV outpatient visits: 3-4	0.58455	0.50947	0.6707	<.0001
118	Indicator, prior non-CV outpatient visits: 5-9	0.67385	0.60603	0.74926	<.0001
119	Indicator, prior non-CV outpatient visits: 10-19	0.77217	0.70148	0.84999	<.0001
120	Any hospital stay 30 days preceding qual admit	0.98928	0.87686	1.11611	0.8609
121	More than 7 inpatient days prior to te	0.92603	0.80184	1.06945	0.2956
122	Clopidogrel/ticlopidene prior to te	1.15245	1.04739	1.26804	0.0036
123	Qualifying event hospital stay days	1.01873	1.00981	1.02773	<.0001

Table A-2. Study findings according to propensity score deciles.

	Gastroduodenal Bleeding Endpoint				Serious Cardiovascular Disease Endpoint			
Propensity score decile	Person-years	Gastro-duodenal bleeds, N	HR: PPI user vs nonuser	95% CI	Person-years	Serious cardiovascular disease, N	HR: PPI user vs nonuser	95% CI
1	1738	14	0.64	0.24-1.73	1539	91	0.99	0.58-1.69
2	1889	20	0.37	0.15-0.91	1739	107	1.02	0.66-1.56
3	1940	23	0.26	0.09-0.71	1793	124	0.89	0.58-1.35
4	1995	16	0.72	0.25-2.10	1841	120	1.36	0.90-2.06
5	1771	15	1.48	0.53-1.45	1676	104	1.09	0.75-1.60
6	1786	15	0.80	0.27-2.37	1708	111	0.70	0.46-1.08
7	1671	14	0.50	0.16-1.61	1590	94	0.66	0.43-1.01
8	1585	20	0.19	0.04-0.82	1517	88	1.36	0.93-1.99
9	1531	19	0.73	0.25-2.10	1458	101	0.93	0.60-1.46
10	1403	24	0.00	undefined	1361	101	1.11	0.67-1.84

Table A-3. Qualifying hospital (hospital from which patient discharged just prior to t_0) volume tertiles. Volume defined as number of cohort patients whose qualifying hospital discharge occurred at that institution. The first tertile consists of cohort patients discharged from the 4 qualifying hospitals with the largest volume, and so on. The numbers of qualifying hospitals for with no endpoints during followup is shown for all patients discharged from that hospital at t_0 and for patients according to PPI use status during followup.

	Qualifying Hospitals				Gastroduodenal (GD) Bleeding			
Tertile	N	N with no followup GD Bleeds			Person-years	GD Bleeds	HR: PPI user vs nonuser	95% CI
		All	PPI nonuser	PPI User				
1	4	0	0	0	5730	63	0.49	0.27-0.89
2	9	0	0	2	5771	46	0.57	0.27-1.18
3	119	89	94	103	5809	71	0.50	0.27-0.93

Table A-4. Cox regression model results for gastroduodenal bleeding hospitalization endpoint. Shown are the hazard ratios (HRs), the 95% confidence intervals (CIs), and the p-value (p).

		HR	*95% CI*		*p*
Age in years, mean		1.0347	1.0223	1.0472	0.0000
Male, %		0.8333	0.6147	1.1298	0.2404
Calendar year of cohort entry, mean 2005	2005	0.9103	0.4216	1.9657	0.8110
Calendar year of cohort entry, mean 2004	2004	0.5474	0.2667	1.1236	0.1005
Calendar year of cohort entry, mean 2003	2003	0.7102	0.3979	1.2676	0.2470
Calendar year of cohort entry, mean 2002	2002	0.6193	0.3508	1.0932	0.0984
Calendar year of cohort entry, mean 2001	2001	0.4287	0.2489	0.7383	0.0023
Calendar year of cohort entry, mean 2000	2000	0.7843	0.4577	1.3440	0.3766
White, %		1.0381	0.7908	1.3626	0.7878
TennCare enrollment uninsured, %		0.8192	0.5382	1.2471	0.3523
Qualifying hospitalization AMI 1	1	1.0554	0.7869	1.4154	0.7189
Propensity score for baseline PPI use, deciles 9	9	2.4952	1.1417	5.4531	0.0219
Propensity score for baseline PPI use, deciles 8	8	1.6091	0.6650	3.8934	0.2913
Propensity score for baseline PPI use, deciles 7	7	1.5786	0.8008	3.1117	0.1874
Propensity score for baseline PPI use, deciles 6	6	1.0804	0.4158	2.8073	0.8739
Propensity score for baseline PPI use, deciles 5	5	1.0847	0.4491	2.6196	0.8566
Propensity score for baseline PPI use, deciles 4	4	1.0832	0.4786	2.4511	0.8480
Propensity score for baseline PPI use, deciles 3	3	1.0729	0.5819	1.9783	0.8217
Propensity score for baseline PPI use, deciles 2	2	1.6107	0.8528	3.0421	0.1418
Propensity score for baseline PPI use, deciles 1	1	1.3329	0.6959	2.5531	0.3861
Followup anticoagulant use 2: Former/indet user	2: Former/indet user	1.3408	0.7406	2.4276	0.3329
Followup anticoagulant use 1: Current user	1: Current user	3.4947	2.3996	5.0894	0.0000
Followup corticosteroid use 2: Former/indet user	2: Former/indet user	1.1153	0.8261	1.5058	0.4761
Followup corticosteroid use 1: Current user	1: Current user	1.8994	1.0334	3.4912	0.0389
Followup NSAID use and dose 3: Former/indet user	3: Former/indet user	1.4803	0.9457	2.3172	0.0862
Followup NSAID use and dose 2: Current, hi dose	2: Current, hi dose	1.9961	1.0617	3.7527	0.0319
Followup NSAID use and dose 1: Current, low dose	1: Current, low dose	1.7063	0.7314	3.9810	0.2164
Followup coxib use and dose 3: Former/indet user	3: Former/indet user	0.7533	0.3684	1.5402	0.4375
Followup coxib use and dose 2: Current, hi dose	2: Current, hi dose	1.3520	0.8010	2.2819	0.2588
Followup coxib use and dose 1: Current, low dose	1: Current, low dose	1.0099	0.3213	3.1743	0.9866
Followup GI/Trauma hosp (not endpoint) 2: <=90 days	2: <=90 days	1.5520	0.6555	3.6748	0.3176
Followup GI/Trauma hosp (not endpoint) 1: 91-365 days	1: 91-365 days	1.1489	0.4820	2.7384	0.7542
Followup cardiovascular hosp 2: <=90 days	2: <=90 days	0.5236	0.2726	1.0055	0.0519
Followup cardiovascular hosp 1: 91-365 days	1: 91-365 days	1.1216	0.6589	1.9094	0.6724
Followup other hosp 2: <=90 days	2: <=90 days	0.7361	0.3543	1.5297	0.4117
Followup other hosp 1: 91-365 days	1: 91-365 days	0.9137	0.6152	1.3569	0.6545
Followup ED visit 2: <=90 days	2: <=90 days	1.3719	0.9922	1.8969	0.0558
Followup ED visit 1: 91-365 days	1: 91-365 days	1.2323	0.8648	1.7560	0.2476
Followup days in hospital past 90 days 4: 15+	4: 15+	4.6060	1.4243	14.8954	0.0108
Followup days in hospital past 90 days 3: 7-14	3: 7-14	2.0859	0.7488	5.8106	0.1596
Followup days in hospital past 90 days 2: 3-7	2: 3-7	2.4530	1.1418	5.2698	0.0215
Followup days in hospital past 90 days 1: 1-2	1: 1-2	2.2249	0.9279	5.3346	0.0731
Followup GI symptoms 1	1	2.1998	1.0028	4.8255	0.0492
Followup low-dose aspirin 2: indet/former	2: indet/former	1.4370	0.8831	2.3383	0.1444
Followup low-dose aspirin 1: current	1: current	1.4879	1.0343	2.1405	0.0322
Overall PPI use status changed from t0		1.0855	0.6925	1.7014	0.7205
Followup PPI use status 3: Current user PPI	3: Current user PPI	0.5026	0.3872	0.6524	0.0000

Table A-5. Cox regression model results for serious cardiovascular disease endpoint. Shown are the hazard ratios (HRs), the 95% confidence intervals (CIs), and the p-value (p).

			HR	*95% CI*		*p*
Age in years, mean			1.019	1.014	1.025	0.003
Male, %			1.071	0.965	1.190	0.054
Calendar year of cohort entry, mean 2005		2005	0.759	0.495	1.163	0.218
Calendar year of cohort entry, mean 2004		2004	0.828	0.615	1.114	0.152
Calendar year of cohort entry, mean 2003		2003	0.872	0.648	1.173	0.151
Calendar year of cohort entry, mean 2002		2002	0.908	0.691	1.192	0.139
Calendar year of cohort entry, mean 2001		2001	0.982	0.767	1.257	0.126
Calendar year of cohort entry, mean 2000		2000	1.085	0.859	1.369	0.119
White, %			0.942	0.820	1.084	0.071
TennCare enrollment uninsured, %			0.830	0.728	0.948	0.067
Clopidogrel/ticlopidene prior to te, %			1.323	1.150	1.522	0.072
Qualifying hospitalization diagnosis 7: AMI, CABG	7: AMI, CABG		0.905	0.595	1.377	0.214
Qualifying hospitalization diagnosis 6: AMI, Stent, DE	6: AMI, Stent, DE		1.541	1.051	2.261	0.195
Qualifying hospitalization diagnosis 5: AMI, Stent, NDE	5: AMI, Stent, NDE		1.245	0.866	1.788	0.185
Qualifying hospitalization diagnosis 4: AMI, Medical	4: AMI, Medical		2.311	1.825	2.927	0.121
Qualifying hospitalization diagnosis 3: No AMI, CABG	3: No AMI, CABG		0.844	0.623	1.144	0.155
Qualifying hospitalization diagnosis 2: No AMI, Stent, DE	2: No AMI, Stent, DE		0.817	0.595	1.121	0.162
Qualifying hospitalization diagnosis 1: No AMI, Stent, NDE	1: No AMI, Stent, NDE		0.925	0.736	1.164	0.117
Propensity score for baseline PPI use, deciles 9		9	1.044	0.731	1.490	0.182
Propensity score for baseline PPI use, deciles 8		8	1.037	0.706	1.524	0.196
Propensity score for baseline PPI use, deciles 7		7	0.877	0.660	1.166	0.145
Propensity score for baseline PPI use, deciles 6		6	0.973	0.731	1.295	0.146
Propensity score for baseline PPI use, deciles 5		5	1.079	0.795	1.463	0.156
Propensity score for baseline PPI use, deciles 4		4	0.941	0.690	1.283	0.158
Propensity score for baseline PPI use, deciles 3		3	1.091	0.832	1.431	0.138
Propensity score for baseline PPI use, deciles 2		2	1.204	0.946	1.532	0.123
Propensity score for baseline PPI use, deciles 1		1	1.004	0.725	1.391	0.166

		HR	*95% CI*		*p*
Followup GI hosp		1.044	0.784	1.391	0.146
Followup cardiovascular hosp (not endpoint)		1.210	0.968	1.513	0.114
Followup other hosp		0.842	0.682	1.041	0.108
Followup, time since last hosp 4: 1-14 days	4: 1-14 days	1.746	1.235	2.470	0.177
Followup, time since last hosp 3: 15-29 days	3: 15-29 days	1.349	0.895	2.035	0.210
Followup, time since last hosp 2: 30-90 days	2: 30-90 days	1.097	0.772	1.560	0.179
Followup, time since last hosp 1: 91-365 days	1: 91-365 days	0.973	0.675	1.404	0.187
Followup, ED in past 365 days		1.387	1.074	1.790	0.130
Followup, Angioplasty		0.832	0.704	0.982	0.085
Followup, Stent		0.910	0.753	1.099	0.096
Followup, CABG		0.700	0.502	0.976	0.170
Followup, new diagnosis heart failure		1.591	1.363	1.857	0.079
Followup, new diagnosis cerebrovascular disease		1.230	1.073	1.410	0.070
Followup, new diagnosis peripheral vascular disease		1.399	1.099	1.780	0.123
Followup, new digoxin start		1.473	1.170	1.855	0.117
Followup, new loop diuretic start		1.080	0.904	1.291	0.091
Followup, new insulin start		1.323	1.027	1.705	0.129
followup, new calcium channel blocker start		0.825	0.662	1.028	0.112
Followup, low-dose aspirin past 365 days		0.845	0.737	0.968	0.069
Followup, statin in past 365 days		0.714	0.622	0.818	0.070
Followup, in hospital 4+ days in past 90		1.665	1.146	2.419	0.191
Followup, days in hospital in past 365 5: 30+ days	5: 30+ days	2.186	1.482	3.224	0.198
Followup, days in hospital in past 365 4: 15-30 days	4: 15-30 days	1.719	1.165	2.536	0.198
Followup, days in hospital in past 365 3: 7-14 days	3: 7-14 days	1.577	1.155	2.153	0.159
Followup, days in hospital in past 365 2: 3-7 days	2: 3-7 days	1.290	0.971	1.715	0.145
Overall PPI use status changed from t0		1.119	0.926	1.351	0.096
Followup PPI use status 3: Current user PPI	3: Current user PPI	0.989	0.821	1.192	0.095

Table A-6. Cohort members whose qualifying hospitalization included percutaneous coronary intervention with stenting. Risk of serious cardiovascular disease endpoints among current users of clopidogrel, according to concurrent use of proton-pump inhibitors (PPIs).[*]

	No Concurrent PPI (5695 py)	*Concurrent PPI (4457 py)*	*HR (95% CI)*	*p*
	N (Rate/1000 py)			
Serious cardiovascular disease	296 (52.0)	228 (51.2)	1.01 (0.77-1.30)	.98
Acute myocardial infarction or sudden cardiac death	219 (38.4)	154 (34.6)	1.00 (0.76-1.30)	.97
Stroke	43 (7.6)	47 (10.5)	0.97 (0.50-1.90)	.94
Other cardiovascular death	34 (6.0)	27 (6.1)	1.22 (0.57-2.56)	.61

[*]HR = hazard ratio, adjusted for potential confounders. py = person-years, CI = confidence interval.

Table A-7. Sensitivity analyses for serious cardiovascular disease endpoint.[*]

	All PPIs		*Pantoprazole*		*Omeprazole*	
	HR	*95% CI*	*HR*	*95% CI*	*HR*	*95% CI*
Primary analysis	0.99	0.82-1.19	1.08	0.88-1.32	0.74	0.54-1.15
New users of clopidogrel, first year of followup[**]						
a. With time-dependent covariates	0.91	0.70-1.19	1.02	0.71-1.46	0.79	0.46-1.36
b. No time-dependent covariates	0.91	0.72-1.15	0.94	0.70-1.28	0.88	0.54-1.43
c. No time-dependent covariates, censored when PPI status changes	0.92	0.72-1.18	0.97	0.69-1.36	0.88	0.55-1.43
Other users of clopidogrel						
a. With time-dependent covariates	0.99	0.81-1.22	1.08	0.87-1.35	0.78	0.50-1.22
b. No time-dependent covariates	1.01	0.83-1.23	1.12	0.88-1.44	0.94	0.72-1.23
c. No time-dependent covariates, censored when PPI status changes	1.05	0.84-1.30	1.18	0.91-1.53	1.00	0.75-1.34
Population comparable to VA study[***]	1.03	0.68-1.56	1.04	0.67-1.61	0.63	0.32-1.26

[*]PPI = Proton-pump inhibitor, HR = hazard ratio for serious cardiovascular disease comparing current users of PPIs to nonusers, adjusted for potential confounders. CI = confidence interval.

[**]New users are defined as persons with no clopidogrel use prior to the qualifying hospital admission and who begin clopidogrel use within seven days of the qualifying hospital discharge. The model without time-dependent covariates uses PPI status as of t_0, the first day of clopidogrel use following the qualifying hospital discharge. One model censors person-time when PPI use status changes from that at baseline.

[***]Males, 55 years of age or older, endpoint is serious cardiovascular disease or death from any cause, clopidogrel use began within seven days of the qualifying hospital discharge. See Ho and colleagues(11).

Table A-8. Sensitivity analyses for gastroduodenal bleeding hospitalization endpoint.[*]

	All PPIs		*Pantoprazole*		*Omeprazole*	
	HR	*95% CI*	*HR*	*95% CI*	*HR*	*95% CI*
Primary analysis	0.50	0.39-0.65	0.46	0.33-0.63	0.43	0.16-1.13
New users of clopidogrel, first year of followup[**]						
a. With time-dependent covariates	0.66	0.39-1.11	0.58	0.29-1.18	0.84	0.23-3.11
b. No time-dependent covariates	0.73	0.44-1.20	0.57	0.27-1.22	0.67	0.15-3.00
c. No time-dependent covariates, censored when PPI status changes	0.75	0.46-1.25	0.58	0.27-1.26	0.72	0.16-3.27
Other users of clopidogrel						
a. With time-dependent covariates	0.45	0.32-0.62	0.42	0.31-0.56	0.25	0.06-1.00
b. No time-dependent covariates	0.54	0.33-0.89	0.32	0.13-0.81	0.48	0.24-0.98
c. No time-dependent covariates, censored when PPI status changes	0.44	0.29-0.67	0.27	0.11-0.62	0.26	0.10-0.66
Population comparable to VA study[***]	0.61	0.26-1.42	0.30	0.09-0.96	0.55	0.39-5.68

[*]PPI = Proton-pump inhibitor, HR = hazard ratio for serious cardiovascular disease comparing current users of PPIs to nonusers, adjusted for potential confounders. CI = confidence interval.

[**]New users are defined as persons with no clopidogrel use prior to the qualifying hospital admission and who begin clopidogrel use within seven days of the qualifying hospital discharge. The model without time-dependent covariates uses PPI status as of t_0, the first day of clopidogrel use following the qualifying hospital discharge. One model censors person-time when PPI use status changes from that at baseline.

[***]Males, 55 years of age or older, endpoint is serious cardiovascular disease or death from any cause, clopidogrel use began within seven days of the qualifying hospital discharge. See Ho and colleagues(11).

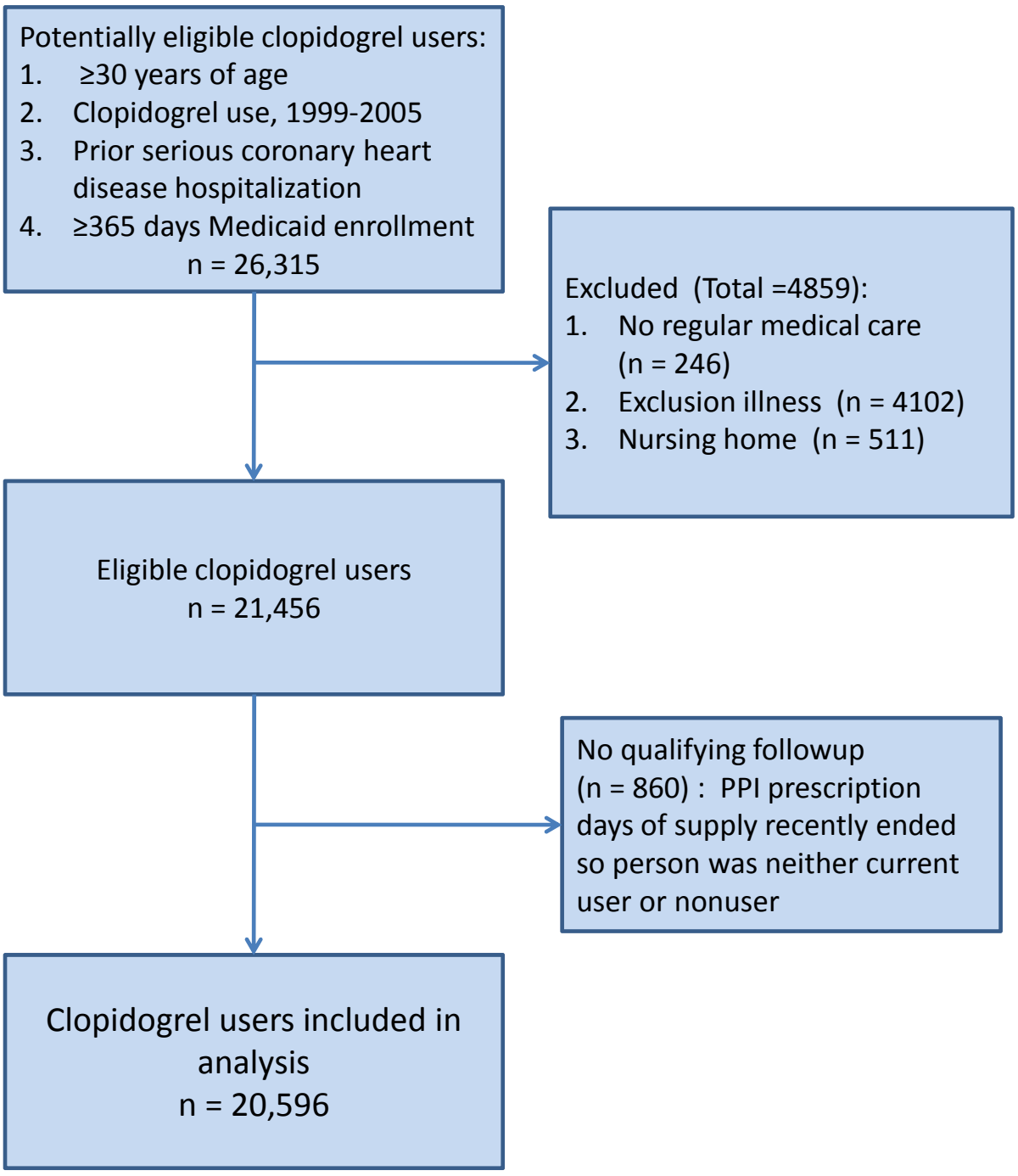

Figure A-1 Study Flow Diagram

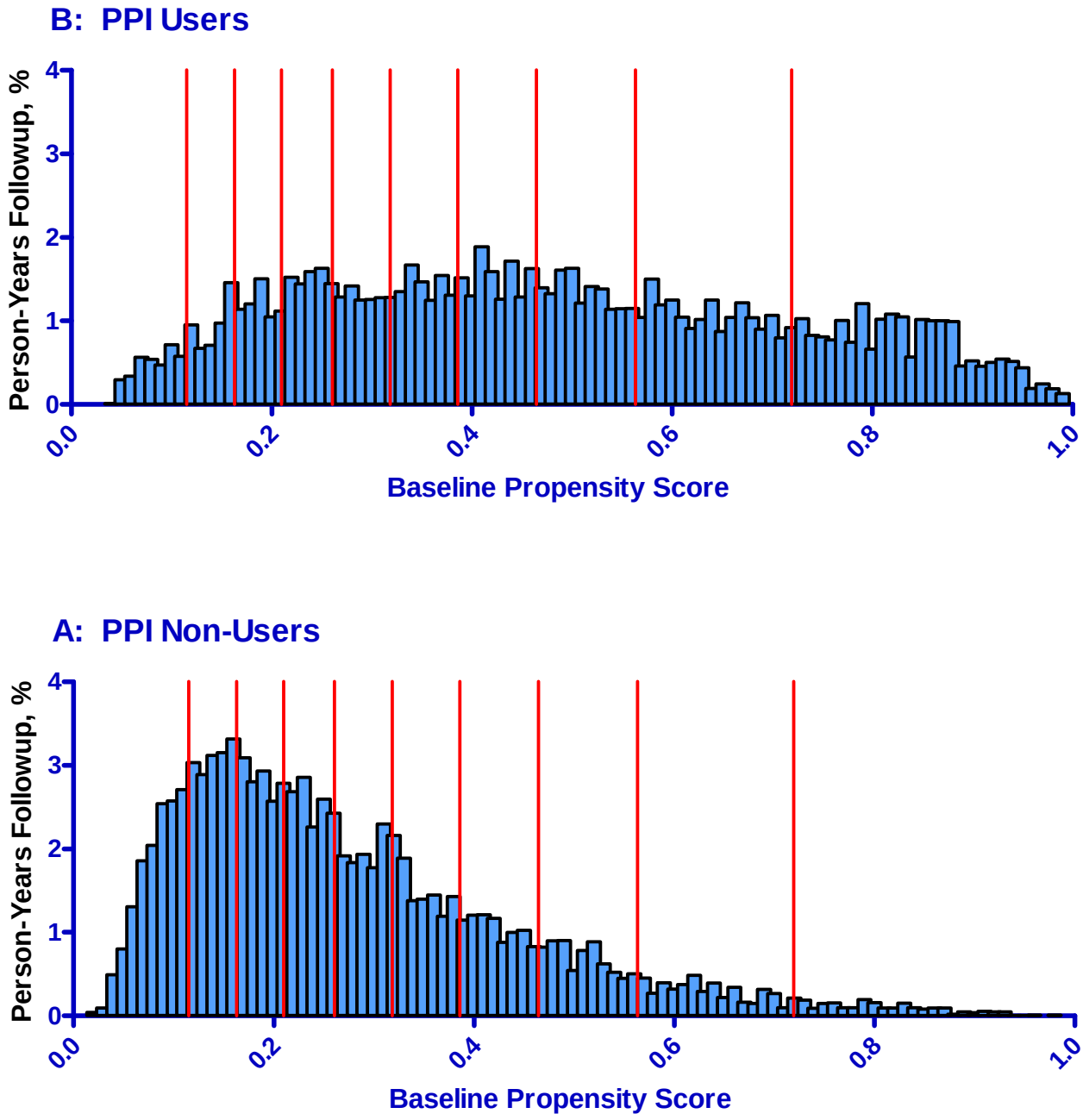

Figure A-2. Distribution of person years of followup according to baseline propensity score (probability of baseline PPI use), for baseline nonusers of PPIs (Panel A) and baseline users of PPIs (Panel B). Red vertical lines indicate deciles for the propensity score.

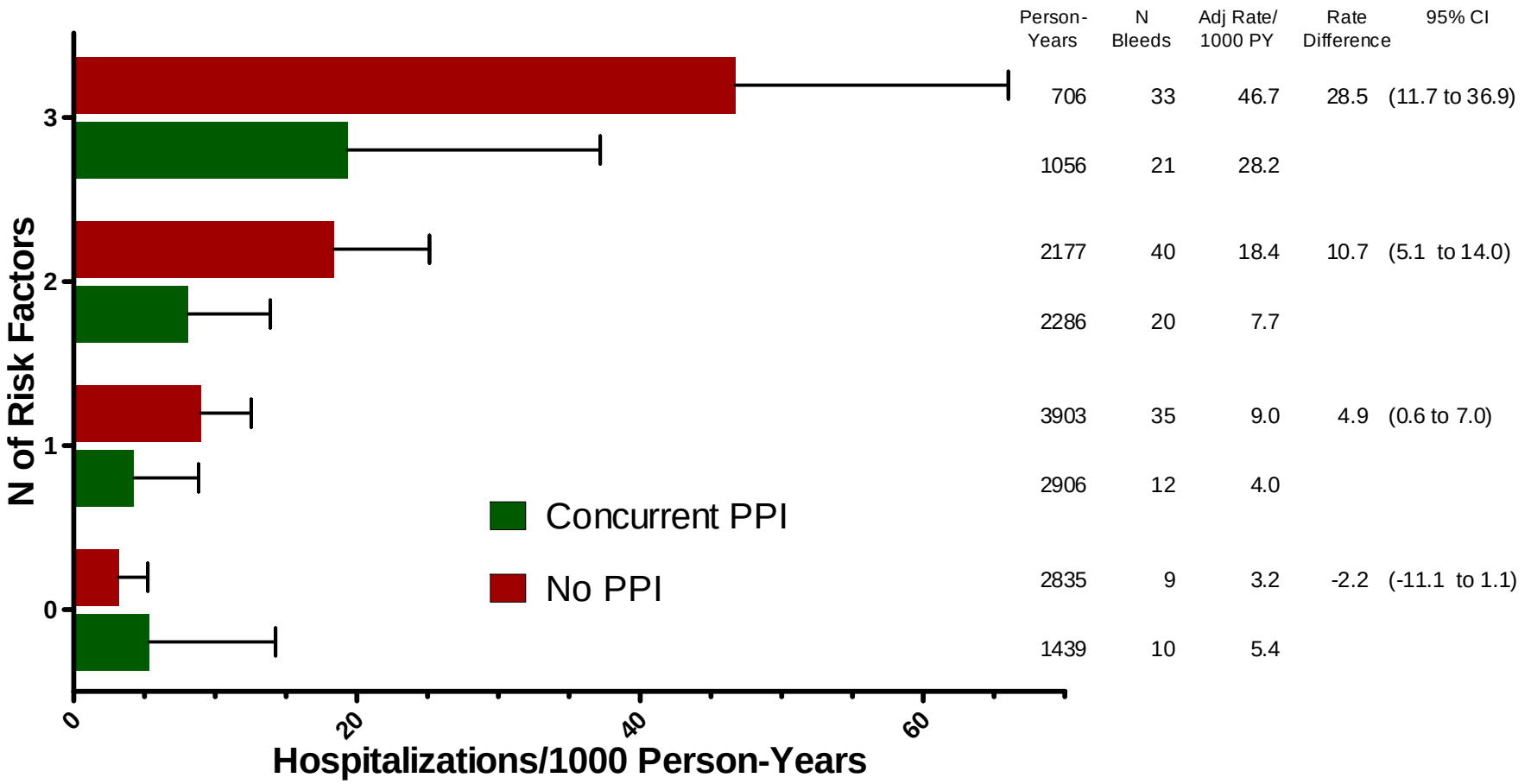

Figure A-3 Risk of gastroduodenal bleeding hospitalizations among current users of clopidogrel, according to concurrent use of proton-pump inhibitors (PPIs). 'Rate Difference' is for nonusers of PPIs versus current users and is adjusted for potential confounders. The individual risk factors are age 65 years or older, prior history of hospitalization for upper gastrointestinal disease or bleeding, recent use of anticoagulants, current use of other medications that increase bleeding risk (systemic corticosteroids, NSAIDs/coxibs), and any hospital discharge in the past year. CI denotes confidence interval.

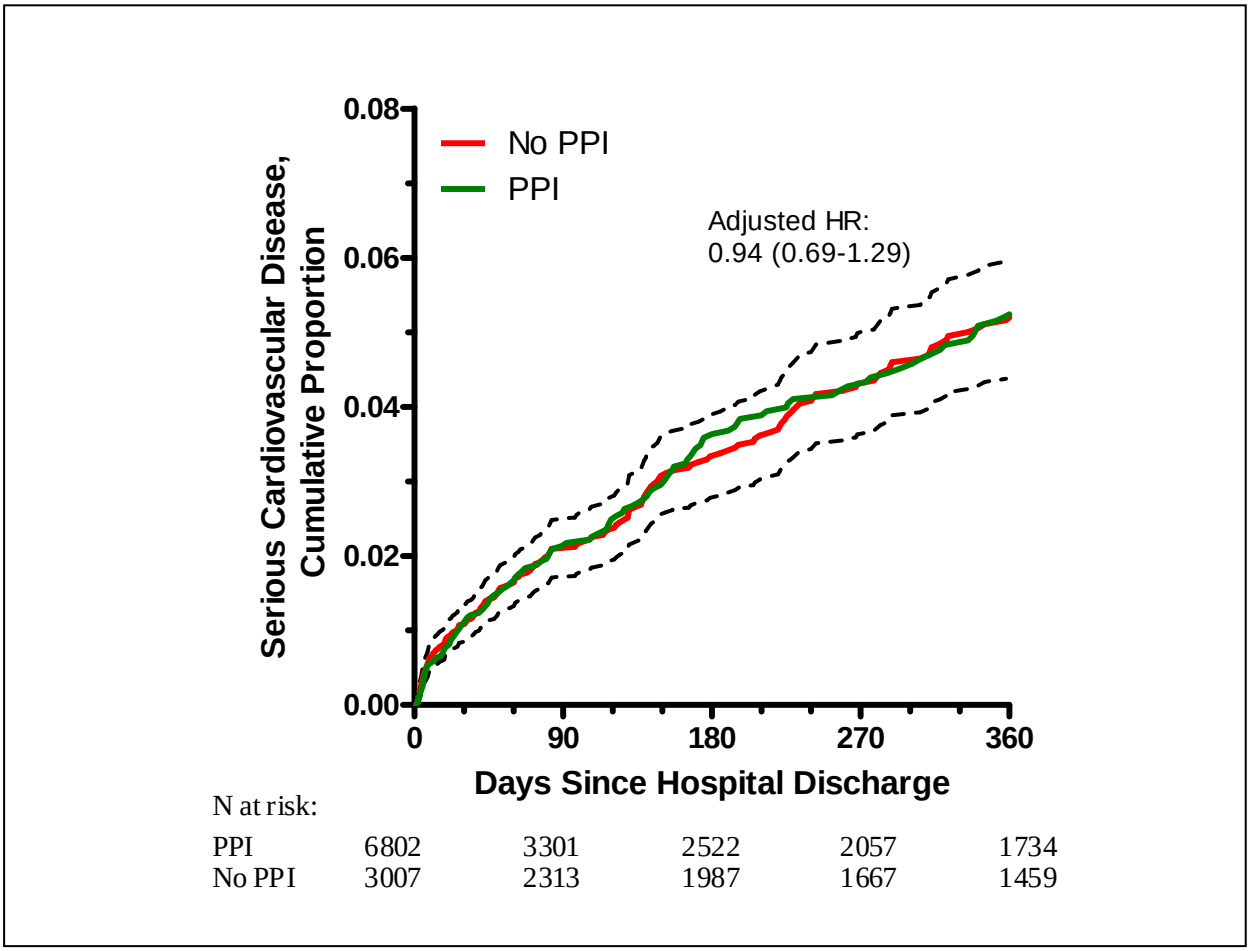

Figure A-4. Risk of serious cardiovascular disease endpoint (nonfatal or fatal myocardial infarction, stroke, or other cardiovascular death) in current clopidogrel users who had had a percutaneous coronary intervention with stenting, according to concurrent PPI use status. Figure shows unadjusted cumulative proportions with serious cardiovascular disease. The dashed line is the 95% confidence interval for the PPI nonuser group. Both clopidogrel and PPI use status could change on each day of followup; thus, the cumulative proportions were calculated using the method of Simon and Makuch.(44) HR is the adjusted hazard ratio, with the 95% confidence interval in parentheses.