

SUPPLEMENTAL MATERIAL

Supplement to: *Comparative risk of ischemic stroke among users of clopidogrel together with individual proton pump inhibitors*

Supplemental Tables

Supplemental Table I. Characteristics of clopidogrel users, by proton pump inhibitor exposure group

		Pantoprazole	Esomeprazole				Lansoprazole			Omeprazole			Rabeprazole		
		N	N				N			N			N		
Users, concomitant with clopidogrel		57,089	59,821				106,470			88,069			14,110		
Person-years of follow-up		12,057	13,359				23,185			18,791			2,882		
Acute ischemic stroke events		350	238				617			408			54		
Characteristic	Group	%	%	SMD	WCSD	%	SMD	WCSD	%	SMD	WCSD	%	SMD	WCSD	
<i>Demographic factors</i>															
Method of cohort entry	clopidogrel added to ongoing PPI therapy	35.1	44.0	0.18	0.13	44.5	0.19	0.16	38.2	0.06	0.10	42.5	0.15	0.13	
	clopidogrel and PPI initiated on same day	30.6	18.9	0.27	0.22	21.1	0.22	0.17	19.7	0.25	0.21	18.0	0.30	0.25	
	PPI added to ongoing clopidogrel therapy	34.3	37.2	0.06	0.08	34.5	0.00	0.06	42.1	0.16	0.11	39.5	0.11	0.10	
Age at cohort entry (continuous) [†]	Median (Q1-Q3)	72.0 (62.4-80.2)	69.7 (59.8-77.5)	0.19	0.13	71.5 (62.1-79.5)	0.04	0.09	72.0 (62.4-80.2)	0.00	0.11	71.5 (62.1-79.5)	0.04	0.11	
Age at cohort entry (deciles)	1	8.5	12.1	0.12	0.10	9.9	0.05	0.06	9.8	0.04	0.06	8.8	0.01	0.06	
	2	8.5	12.0	0.11	0.08	9.9	0.05	0.07	9.8	0.04	0.07	8.8	0.01	0.04	
	3	8.6	11.2	0.09	0.07	10.5	0.06	0.07	9.6	0.04	0.07	9.3	0.03	0.02	
	4	9.5	10.4	0.03	0.05	10.1	0.02	0.03	9.9	0.01	0.02	10.1	0.02	0.02	
	5	9.7	10.6	0.03	0.04	9.9	0.01	0.03	9.8	0.00	0.03	11.1	0.04	0.03	

	6	10.0	10.1	0.00	0.03	9.9	0.00	0.04	9.6	0.01	0.03	11.8	0.06	0.01
	7	10.4	9.7	0.03	0.05	10.0	0.01	0.04	9.8	0.02	0.04	10.8	0.01	0.01
	8	11.1	9.0	0.07	0.04	9.8	0.04	0.03	10.0	0.04	0.03	10.7	0.01	0.01
	9	11.5	8.3	0.11	0.04	9.9	0.05	0.04	10.4	0.03	0.04	9.8	0.05	0.03
	10	12.1	6.6	0.19	0.03	10.0	0.07	0.05	11.2	0.03	0.06	8.8	0.11	0.07
Sex	female	63.9	62.7	0.03	0.06	64.3	0.01	0.02	63.0	0.02	0.01	64.8	0.02	0.02
Race†	white	49.6	44.8	0.10	0.16	46.8	0.06	0.03	48.7	0.02	0.13	44.1	0.11	0.09
	black	14.3	12.7	0.05	0.12	13.2	0.03	0.09	13.2	0.03	0.06	9.0	0.17	0.08
	other / unknown	36.0	42.5	0.13	0.16	40.0	0.08	0.08	38.2	0.04	0.14	47.0	0.22	0.08
State of residence†	CA	39.1	32.5	0.14	0.22	34.4	0.10	0.06	32.4	0.14	0.16	45.4	0.13	0.14
	FL	15.9	12.3	0.10	0.13	26.1	0.25	0.12	12.4	0.10	0.17	10.0	0.17	0.20
	NY	27.6	36.8	0.20	0.26	23.1	0.10	0.25	32.4	0.10	0.17	33.5	0.13	0.20
	OH	6.7	14.3	0.25	0.13	11.2	0.16	0.17	8.3	0.06	0.14	6.6	0.00	0.11
	PA	10.7	4.1	0.25	0.09	5.1	0.21	0.07	14.5	0.12	0.10	4.5	0.24	0.07
Calendar year of cohort entry†	2000/2001	5.0	1.2	0.22	0.01	14.6	0.33	0.01	12.5	0.27	0.01	17.8	0.41	0.01
	2002	12.9	5.0	0.28	0.11	11.2	0.05	0.11	4.0	0.32	0.19	17.7	0.14	0.15
	2003	14.9	7.5	0.24	0.10	15.6	0.02	0.10	3.4	0.41	0.07	13.6	0.04	0.05
	2004	15.8	9.8	0.18	0.16	10.4	0.16	0.07	3.9	0.41	0.13	14.9	0.02	0.09
	2005	7.1	16.1	0.28	0.29	16.2	0.28	0.08	5.8	0.05	0.23	7.1	0.00	0.03
	2006	13.8	17.1	0.09	0.20	12.8	0.03	0.12	16.9	0.09	0.19	9.4	0.14	0.11
	2007	12.0	15.5	0.10	0.13	9.5	0.08	0.08	16.1	0.12	0.20	8.4	0.12	0.11
	2008	9.0	13.3	0.14	0.05	4.8	0.16	0.03	16.3	0.22	0.09	6.4	0.10	0.06
	2009	9.5	14.6	0.16	0.08	4.9	0.18	0.07	21.1	0.33	0.08	4.8	0.18	0.06
CMS dual-eligible†	Yes	84.5	72.6	0.29	0.24	76.6	0.20	0.22	80.3	0.11	0.20	80.9	0.10	0.08
<i>Health system use factors</i>														

ACS hospitalization 29 days prior to cohort entry	Yes	15.5	8.8	0.21	0.17	10.6	0.14	0.09	9.2	0.19	0.11	7.5	0.25	0.15
Nursing home residence, ever during baseline†	Yes	31.5	15.2	0.39	0.08	25.4	0.14	0.15	27.2	0.10	0.11	13.1	0.45	0.11
# circulatory system hospitalizations in prior year (continuous)	Median (Q1-Q3)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.03	0.17	0.0 (0.0-1.0)	0.08	0.15	0.0 (0.0-1.0)	0.00	0.14	0.0 (0.0-1.0)	0.08	0.19
# circulatory system hospitalizations in prior year†	0	46.2	62.3	0.33	0.26	57.8	0.23	0.15	60.5	0.29	0.16	64.7	0.38	0.22
	1	33.4	26.1	0.16	0.19	27.7	0.12	0.08	27.3	0.13	0.11	24.3	0.20	0.15
	2	12.7	7.9	0.16	0.14	9.5	0.10	0.07	8.4	0.14	0.08	7.6	0.17	0.11
	3+	7.7	3.7	0.17	0.12	5.0	0.11	0.09	3.8	0.17	0.09	3.4	0.19	0.13
# non-circulatory system hospitalizations in prior year (continuous)	Median (Q1-Q3)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.06	0.15	0.0 (0.0-1.0)	0.07	0.13	0.0 (0.0-1.0)	0.00	0.14	0.0 (0.0-1.0)	0.07	0.22
# non-circulatory system hospitalizations in prior year†	0	48.5	67.1	0.38	0.24	60.1	0.23	0.13	63.0	0.29	0.16	70.4	0.46	0.18
	1	26.8	19.6	0.17	0.18	22.1	0.11	0.08	21.1	0.13	0.12	18.7	0.19	0.14
	2	12.4	7.0	0.18	0.12	9.0	0.11	0.05	8.4	0.13	0.08	6.2	0.22	0.08
	3+	12.2	6.2	0.21	0.15	8.7	0.11	0.10	7.4	0.16	0.10	4.7	0.27	0.14
# circulatory system ED visits in prior year (continuous)	Median (Q1-Q3)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.00	0.01	0.0 (0.0-1.0)	0.03	0.03	0.0 (0.0-1.0)	0.00	0.03	0.0 (0.0-1.0)	0.03	0.04
# circulatory system ED visits in prior year†	0	58.3	72.6	0.31	0.20	67.3	0.19	0.14	70.3	0.25	0.15	74.7	0.35	0.15
	1	24.9	18.1	0.17	0.15	20.9	0.10	0.08	19.4	0.13	0.09	17.1	0.19	0.11
	2	9.3	5.5	0.15	0.11	6.7	0.09	0.06	6.2	0.12	0.09	4.6	0.18	0.08
	3+	7.5	3.8	0.16	0.10	5.1	0.10	0.07	4.1	0.14	0.08	3.5	0.18	0.09
# non-circulatory system ED visits in prior year (continuous)	Median (Q1-Q3)	1.0 (0.0-2.0)	1.0 (0.0-2.0)	0.01	0.06	1.0 (0.0-2.0)	0.05	0.07	1.0 (0.0-2.0)	0.00	0.06	1.0 (0.0-2.0)	0.05	0.08
# non-circulatory system	0	30.0	45.6	0.33	0.22	39.6	0.20	0.16	44.1	0.29	0.12	49.6	0.41	0.16

ED visits in prior year†	1	23.1	21.6	0.04	0.11	22.5	0.01	0.05	21.2	0.05	0.05	21.5	0.04	0.10
	2	15.5	12.1	0.10	0.09	13.5	0.06	0.04	12.7	0.08	0.05	12.0	0.10	0.08
	3+	31.4	20.7	0.25	0.16	24.4	0.16	0.11	22.1	0.21	0.13	17.0	0.34	0.13
# circulatory system outpatient visits in prior year (continuous)	Median (Q1-Q3)	6.0 (2.0-13.0)	7.0 (3.0-13.0)	0.07	0.04	8.0 (4.0-15.0)	0.08	0.06	6.0 (2.0-13.0)	0.00	0.05	8.0 (4.0-15.0)	0.08	0.06
# circulatory system outpatient visits in prior year (deciles)†	1	12.6	15.6	0.09	0.08	11.8	0.03	0.14	20.6	0.21	0.07	14.5	0.05	0.12
	2	4.8	6.8	0.09	0.03	6.0	0.05	0.02	6.2	0.06	0.03	6.3	0.07	0.02
	3	10.5	14.0	0.11	0.04	12.7	0.07	0.03	12.6	0.07	0.03	13.9	0.10	0.03
	4	10.8	12.7	0.06	0.02	12.2	0.04	0.02	11.6	0.03	0.02	13.1	0.07	0.03
	5	5.0	5.9	0.04	0.01	5.6	0.03	0.01	5.0	0.00	0.02	5.9	0.04	0.02
	6	9.1	9.4	0.01	0.02	9.6	0.02	0.01	8.6	0.02	0.02	10.0	0.03	0.02
	7	11.4	10.2	0.04	0.05	11.1	0.01	0.03	9.7	0.06	0.04	10.7	0.02	0.03
	8	11.0	8.2	0.09	0.06	9.9	0.03	0.04	8.4	0.09	0.06	9.0	0.07	0.04
	9	13.2	8.3	0.16	0.07	11.0	0.07	0.07	9.4	0.12	0.08	8.3	0.16	0.06
	10	11.6	8.9	0.09	0.05	10.2	0.04	0.07	7.8	0.13	0.06	8.2	0.11	0.07
# non-circulatory system outpatient visits in prior year (continuous)	Median (Q1-Q3)	23.0 (10.0-45.0)	26.0 (14.0-52.0)	0.14	0.11	28.0 (15.0-52.0)	0.10	0.12	23.0 (10.0-45.0)	0.00	0.10	28.0 (15.0-52.0)	0.10	0.14
# non-circulatory system outpatient visits in prior year (deciles)†	1	10.2	9.4	0.03	0.09	7.0	0.11	0.10	15.8	0.17	0.06	8.9	0.04	0.11
	2	9.8	11.2	0.05	0.06	10.3	0.02	0.04	11.5	0.06	0.05	12.5	0.09	0.08
	3	9.7	10.8	0.04	0.05	10.4	0.02	0.03	10.3	0.02	0.03	12.3	0.08	0.06
	4	9.7	10.2	0.02	0.02	10.3	0.02	0.01	9.5	0.01	0.01	10.9	0.04	0.04
	5	8.6	8.7	0.00	0.01	9.2	0.02	0.01	8.2	0.01	0.01	9.9	0.05	0.03
	6	10.0	9.8	0.01	0.03	10.5	0.01	0.02	9.2	0.03	0.02	10.4	0.01	0.02
	7	10.5	9.4	0.04	0.03	11.0	0.01	0.03	9.4	0.04	0.03	10.1	0.01	0.02
	8	10.4	8.8	0.05	0.05	10.6	0.01	0.04	8.6	0.06	0.05	9.1	0.05	0.07

	9	11.1	9.5	0.05	0.06	10.6	0.02	0.07	8.9	0.08	0.06	8.2	0.10	0.10
	10	9.9	12.2	0.08	0.10	10.1	0.01	0.09	8.7	0.04	0.07	7.7	0.07	0.08
# unique drugs prescribed in prior year (continuous)	Median (Q1-Q3)	16.0 (11.0-23.0)	18.0 (13.0-25.0)	0.20	0.12	18.0 (13.0-24.0)	0.17	0.08	16.0 (11.0-23.0)	0.00	0.08	18.0 (13.0-24.0)	0.17	0.09
# unique drugs prescribed in prior year (deciles)	1	13.6	9.9	0.12	0.05	9.8	0.12	0.03	13.6	0.00	0.03	10.0	0.11	0.05
	2	11.0	10.2	0.03	0.05	10.2	0.03	0.04	12.0	0.03	0.04	11.1	0.00	0.04
	3	9.1	8.3	0.03	0.04	8.7	0.01	0.02	9.5	0.02	0.02	8.7	0.01	0.02
	4	9.4	9.2	0.01	0.03	9.6	0.00	0.01	10.1	0.02	0.03	9.4	0.00	0.03
	5	9.2	9.1	0.00	0.04	9.8	0.02	0.01	9.7	0.02	0.02	9.5	0.01	0.01
	6	12.9	13.4	0.02	0.01	13.3	0.01	0.01	12.9	0.00	0.02	13.4	0.02	0.02
	7	7.1	7.8	0.02	0.02	7.7	0.02	0.01	7.1	0.00	0.01	7.7	0.02	0.02
	8	8.9	9.8	0.03	0.03	9.7	0.03	0.03	8.6	0.01	0.03	9.3	0.01	0.02
	9	9.5	10.7	0.04	0.03	10.7	0.04	0.03	8.8	0.02	0.03	10.6	0.04	0.04
	10	9.2	11.6	0.08	0.09	10.5	0.05	0.06	7.7	0.05	0.06	10.2	0.04	0.07
<i>Diseases and Procedures</i>														
Alcohol abuse	Yes	8.3	8.8	0.02	0.04	7.5	0.03	0.02	7.6	0.02	0.02	6.1	0.08	0.07
Angina pectoris	Yes	46.0	48.2	0.04	0.10	45.4	0.01	0.07	41.0	0.10	0.08	45.8	0.00	0.09
Artery, arteriole, capillary disease	Yes	62.3	58.3	0.08	0.10	60.4	0.04	0.08	57.0	0.11	0.10	54.2	0.16	0.10
Asthma, COPD, or emphysema	Yes	55.2	54.7	0.01	0.08	54.9	0.01	0.06	50.5	0.09	0.08	49.6	0.11	0.09
Cancer	Yes	30.4	30.0	0.01	0.06	29.2	0.02	0.04	27.9	0.05	0.07	29.6	0.02	0.04
Cerebrovascular disease, CAO and stenosis	Yes	31.9	30.9	0.02	0.08	31.7	0.00	0.08	27.8	0.09	0.08	29.1	0.06	0.06
Cerebrovascular disease, hemorrhage	Yes	4.4	3.0	0.08	0.02	3.7	0.04	0.03	3.6	0.04	0.03	2.7	0.09	0.03
Cerebrovascular disease, ischemic stroke	Yes	40.2	29.5	0.23	0.04	36.8	0.07	0.07	34.6	0.12	0.04	31.6	0.18	0.09

Cerebrovascular disease, other	Yes	52.3	46.5	0.11	0.07	50.6	0.03	0.04	47.0	0.10	0.07	45.8	0.13	0.08
Cerebrovascular disease, other (w/o CAO or stenosis)	Yes	39.3	31.1	0.17	0.05	35.1	0.09	0.05	35.2	0.08	0.06	30.9	0.18	0.07
Cerebrovascular disease, transient cerebral ischemia	Yes	29.6	25.4	0.10	0.05	29.1	0.01	0.04	26.3	0.07	0.05	26.4	0.07	0.05
Cardiac dysrhythmias, all	Yes	61.4	54.1	0.15	0.10	55.8	0.11	0.07	53.2	0.17	0.10	51.9	0.19	0.09
Cardiac dysrhythmias, atrial fibrillation or flutter	Yes	28.9	20.0	0.21	0.08	22.4	0.15	0.05	23.0	0.13	0.09	19.8	0.21	0.06
Cardiac dysrhythmias, other	Yes	55.2	49.7	0.11	0.09	50.6	0.09	0.07	47.4	0.16	0.10	47.1	0.16	0.09
Cardiovascular system symptoms†	Yes	53.9	55.7	0.04	0.10	53.7	0.01	0.10	48.7	0.11	0.11	50.5	0.07	0.11
Circulatory system disease, other	Yes	96.9	97.2	0.02	0.04	97.7	0.05	0.06	95.3	0.08	0.06	96.8	0.00	0.08
Conduction disorder	Yes	19.3	13.9	0.15	0.06	15.3	0.11	0.03	15.5	0.10	0.07	13.3	0.16	0.04
Congenital anomaly of heart	Yes	14.2	12.4	0.05	0.06	13.1	0.03	0.06	11.1	0.09	0.06	11.9	0.07	0.03
Diabetes mellitus	Yes	67.2	67.4	0.00	0.08	65.4	0.04	0.06	65.3	0.04	0.05	62.5	0.10	0.07
Disorder of stomach and duodenum, other*	Yes	4.7	4.8	0.01	0.03	4.0	0.03	0.02	3.9	0.04	0.05	4.4	0.02	0.02
Dyspepsia and other disorders of stomach function*	Yes	20.6	24.7	0.10	0.07	23.5	0.07	0.04	19.9	0.02	0.05	23.9	0.08	0.06
Esophageal disease*	Yes	51.3	58.3	0.14	0.10	52.7	0.03	0.03	52.2	0.02	0.10	54.4	0.06	0.09
Gastrin secretion abnormality*	Yes	0.0	0.0	0.00	0.01	0.0	0.01	0.01	0.0	0.01	0.01	0.0	0.01	0.01
Gastritis/duodenitis*	Yes	42.7	49.4	0.13	0.09	47.4	0.09	0.05	39.6	0.06	0.08	49.0	0.13	0.09
Heart failure or cardiomyopathy†	Yes	63.9	52.9	0.22	0.12	56.7	0.15	0.10	53.5	0.21	0.12	49.7	0.29	0.11

HIV/AIDS	Yes	1.9	2.4	0.04	0.05	2.2	0.02	0.03	1.6	0.02	0.02	1.2	0.06	0.04
Hypertension	Yes	93.1	93.7	0.02	0.06	93.5	0.01	0.07	91.1	0.08	0.05	92.3	0.03	0.09
Hypothyroidism	Yes	37.0	38.2	0.02	0.10	36.3	0.01	0.07	34.8	0.05	0.08	37.4	0.01	0.08
Ischemic heart disease†	Yes	82.4	79.0	0.08	0.11	78.5	0.10	0.09	76.8	0.14	0.09	76.7	0.14	0.09
Lipoid metabolism disorder†	Yes	80.5	86.4	0.16	0.11	79.6	0.02	0.11	79.9	0.01	0.08	81.9	0.04	0.09
Mental disorder, depression	Yes	42.2	44.0	0.04	0.08	44.8	0.05	0.05	41.6	0.01	0.04	36.0	0.13	0.10
Mental disorder, other†	Yes	61.4	60.3	0.02	0.07	60.8	0.01	0.04	58.9	0.05	0.05	51.8	0.19	0.12
MI, acute†	Yes	37.0	26.6	0.23	0.14	27.8	0.20	0.07	28.2	0.19	0.10	23.5	0.30	0.10
MI, old	Yes	25.0	18.8	0.15	0.10	19.5	0.13	0.05	20.7	0.10	0.06	16.7	0.20	0.09
Nervous system disease, disorders of the eye and adnexa	Yes	81.1	84.9	0.10	0.05	83.7	0.07	0.05	78.9	0.05	0.06	83.5	0.06	0.06
Nervous system disease, hereditary and degenerative	Yes	28.4	23.0	0.12	0.07	25.7	0.06	0.04	25.8	0.06	0.05	21.2	0.17	0.10
Nervous system disease: inflammatory disease	Yes	1.5	1.2	0.02	0.03	1.3	0.02	0.03	1.3	0.02	0.02	0.8	0.06	0.04
Nervous system disease, other†	Yes	33.7	29.1	0.10	0.06	31.7	0.04	0.05	29.6	0.09	0.05	26.2	0.16	0.11
Nervous system disease, peripheral	Yes	37.3	41.0	0.08	0.07	37.2	0.00	0.07	35.8	0.03	0.08	35.1	0.05	0.08
Obesity	Yes	20.0	20.5	0.01	0.06	18.0	0.05	0.03	19.6	0.01	0.04	14.6	0.14	0.08
Pulmonary congestion or hypostasis	Yes	19.9	12.0	0.22	0.10	15.0	0.13	0.07	14.6	0.14	0.08	9.0	0.32	0.08
Pacemaker/ICD	Yes	5.5	3.5	0.10	0.06	3.8	0.08	0.04	4.0	0.07	0.05	3.2	0.11	0.04
Renal disease, acute†	Yes	21.3	12.5	0.24	0.14	13.8	0.20	0.07	15.3	0.16	0.11	8.5	0.37	0.13
Renal disease, chronic†	Yes	24.2	16.6	0.19	0.11	16.5	0.19	0.08	19.4	0.12	0.12	12.2	0.32	0.13

Renal failure, other†	Yes	47.1	41.5	0.11	0.09	41.3	0.12	0.07	39.6	0.15	0.10	35.9	0.23	0.12
Stent, carotid or carotid revascularization	Yes	2.9	2.2	0.05	0.06	2.2	0.05	0.03	2.3	0.04	0.04	2.1	0.05	0.05
Stent, coronary†	Yes	25.7	23.3	0.05	0.18	19.4	0.15	0.08	22.5	0.08	0.09	19.2	0.16	0.16
Stent, other vascular†	Yes	11.6	11.1	0.02	0.16	6.5	0.18	0.10	12.6	0.03	0.12	6.2	0.19	0.11
Substance abuse†	Yes	19.4	21.1	0.04	0.12	17.1	0.06	0.04	18.8	0.02	0.05	12.9	0.18	0.12
Tobacco use†	Yes	25.7	26.6	0.02	0.14	21.7	0.09	0.06	24.5	0.03	0.06	17.4	0.20	0.13
Ulcer, duodenal, gastric, gastrojejunal, or peptic*	Yes	24.3	25.6	0.03	0.06	24.8	0.01	0.05	20.9	0.08	0.08	27.9	0.08	0.08
<i>Drug markers of chronic diseases</i>														
Antiadrenergic agent	Yes	27.9	28.0	0.00	0.07	26.7	0.03	0.06	25.1	0.06	0.07	24.6	0.07	0.08
Antialcohol agent	Yes	0.1	0.2	0.02	0.01	0.1	0.00	0.01	0.1	0.00	0.01	0.0	0.03	0.03
Antiarrhythmic agent	Yes	6.2	4.9	0.06	0.04	5.1	0.05	0.02	4.7	0.07	0.04	4.7	0.07	0.02
Anticoagulant	Yes	16.7	12.3	0.13	0.08	13.7	0.08	0.04	14.0	0.08	0.06	10.2	0.19	0.07
Anticonvulsant	Yes	12.6	13.1	0.02	0.05	13.2	0.02	0.04	12.3	0.01	0.01	10.4	0.07	0.07
Antidepressant	Yes	55.1	59.4	0.09	0.06	59.0	0.08	0.03	55.4	0.01	0.02	53.4	0.03	0.05
Antidiabetic agent, insulin	Yes	23.5	18.8	0.12	0.06	20.7	0.07	0.07	21.8	0.04	0.04	14.5	0.23	0.09
Antidiabetic agent, non-insulin	Yes	40.1	40.0	0.00	0.05	38.4	0.04	0.03	39.8	0.01	0.01	35.7	0.09	0.04
Agent for migraine	Yes	2.8	5.7	0.15	0.01	3.9	0.07	0.01	3.2	0.03	0.01	4.5	0.09	0.03
Antiobesity agents	Yes	0.2	0.3	0.01	0.03	0.3	0.01	0.02	0.2	0.00	0.02	0.3	0.02	0.02
Antiplatelet agent (excluding clopidogrel)	Yes	9.8	11.3	0.05	0.04	11.2	0.04	0.03	9.2	0.02	0.03	10.5	0.02	0.03
Antipsychotic	Yes	23.4	24.2	0.02	0.06	25.7	0.05	0.03	22.5	0.02	0.03	19.9	0.08	0.09
Antiretroviral agent	Yes	0.8	1.2	0.04	0.06	1.0	0.02	0.02	0.7	0.01	0.02	0.6	0.03	0.03
Aspirin (low dose)†	Yes	35.6	45.7	0.21	0.14	37.8	0.05	0.06	35.6	0.00	0.04	41.3	0.12	0.06

Beta-adrenergic or alpha/beta-adrenergic blocking agent	Yes	66.5	67.9	0.03	0.08	61.9	0.09	0.04	66.8	0.01	0.04	61.2	0.11	0.03
Bronchodilator or inhaled corticosteroid	Yes	45.6	49.5	0.08	0.05	46.8	0.02	0.03	44.7	0.02	0.04	43.2	0.05	0.06
Calcium channel blocker	Yes	58.2	58.0	0.00	0.07	57.5	0.01	0.06	54.5	0.07	0.06	57.7	0.01	0.07
Diuretic, loop	Yes	47.1	38.9	0.17	0.10	42.2	0.10	0.04	41.0	0.12	0.08	35.6	0.24	0.08
Diuretic, other	Yes	47.9	53.4	0.11	0.05	47.6	0.01	0.04	47.9	0.00	0.04	47.4	0.01	0.04
Fibrate	Yes	10.4	13.5	0.10	0.05	11.1	0.02	0.03	11.3	0.03	0.02	11.2	0.03	0.01
Inotropic agent	Yes	15.9	10.5	0.16	0.06	14.5	0.04	0.03	11.9	0.11	0.04	12.5	0.10	0.03
Leukotriene inhibitor	Yes	10.5	17.0	0.19	0.03	12.6	0.06	0.04	11.0	0.02	0.03	13.2	0.08	0.05
Potassium supplement	Yes	32.5	26.5	0.13	0.09	29.9	0.06	0.03	28.1	0.10	0.06	24.1	0.19	0.05
Ranolazine	Yes	0.3	0.5	0.03	0.01	0.1	0.03	0.01	0.5	0.03	0.02	0.3	0.00	0.01
Renin angiotensin system antagonist	Yes	75.5	77.3	0.04	0.07	73.5	0.04	0.04	74.2	0.03	0.03	72.9	0.06	0.04
Statin	Yes	65.9	74.4	0.19	0.10	64.6	0.03	0.05	70.0	0.09	0.03	66.3	0.01	0.05
Varenicline	Yes	0.7	1.9	0.11	0.02	0.6	0.01	0.02	1.6	0.09	0.01	0.3	0.05	0.03
Vasodilator	Yes	52.5	50.1	0.05	0.08	50.4	0.04	0.04	48.2	0.09	0.06	50.7	0.04	0.06
Thyroid hormone	Yes	15.6	14.1	0.04	0.05	14.0	0.05	0.03	15.1	0.02	0.03	13.4	0.06	0.01
<i>Recent drug exposures</i>														
Alpha/beta-adrenergic blocking agent	Yes	7.1	7.2	0.00	0.05	5.8	0.05	0.03	7.1	0.00	0.04	4.9	0.09	0.04
Antidepressant, MAOI / other	Yes	3.2	4.1	0.05	0.03	4.0	0.04	0.03	3.9	0.04	0.03	3.4	0.01	0.03
Antidepressant, SNRI	Yes	2.1	2.9	0.05	0.03	2.3	0.01	0.01	2.5	0.03	0.02	1.7	0.03	0.02
Antidepressant, SSRI	Yes	13.2	13.7	0.02	0.05	15.4	0.06	0.03	14.1	0.03	0.04	12.3	0.03	0.07
Antidepressant, tetracyclic	Yes	2.0	1.4	0.05	0.05	2.1	0.00	0.04	2.3	0.02	0.04	1.4	0.04	0.04
Antidepressant, tricyclic	Yes	2.8	3.2	0.02	0.02	3.5	0.04	0.02	3.4	0.04	0.03	3.6	0.05	0.02

Antidiabetic agent, thiazolidinedione	Yes	11.0	16.4	0.16	0.03	13.5	0.08	0.02	13.6	0.08	0.04	14.7	0.11	0.03
Anti-infective agent	Yes	39.7	40.7	0.02	0.06	41.7	0.04	0.03	37.9	0.04	0.05	39.8	0.00	0.04
Antipsychotic, benzisoxazole	Yes	2.1	1.7	0.03	0.04	2.6	0.03	0.03	2.0	0.01	0.03	1.4	0.05	0.02
Antipsychotic, dibenzapine	Yes	3.7	3.7	0.00	0.04	4.5	0.04	0.03	3.7	0.00	0.03	2.7	0.05	0.04
Antipsychotic, phenothiazine	Yes	1.0	0.9	0.02	0.02	1.1	0.00	0.01	1.1	0.00	0.01	1.0	0.01	0.01
Antipsychotic, phenylbutylpiperadine	Yes	0.4	0.3	0.02	0.02	0.4	0.00	0.02	0.4	0.01	0.02	0.3	0.02	0.03
Antipsychotic, quinolinone	Yes	0.4	0.7	0.04	0.02	0.6	0.03	0.01	0.6	0.03	0.02	0.2	0.03	0.02
Antipsychotic, thioxanthine	Yes	0.0	0.0	0.00	0.01	0.1	0.00	0.01	0.1	0.00	0.01	0.1	0.01	0.02
Aspirin	Yes	12.3	13.3	0.03	0.07	14.3	0.06	0.05	10.9	0.04	0.05	14.3	0.06	0.09
Beta-adrenergic blocking agent	Yes	26.9	28.3	0.03	0.04	26.5	0.01	0.03	29.9	0.07	0.06	26.2	0.02	0.06
Calcium channel blocking agent	Yes	21.8	23.2	0.03	0.01	23.5	0.04	0.02	22.9	0.03	0.02	23.4	0.04	0.02
Centrally-acting antiadrenergic agent or reserpine	Yes	4.0	3.4	0.03	0.04	3.9	0.00	0.04	3.4	0.03	0.03	2.4	0.09	0.04
CYP2C19 inhibitor	Yes	1.9	1.9	0.00	0.02	2.4	0.03	0.02	2.5	0.04	0.02	2.0	0.01	0.02
CYP3A4 inhibitor	Yes	8.2	6.8	0.05	0.03	8.4	0.01	0.02	7.6	0.02	0.03	8.2	0.00	0.03
CYP3A4 inducer	Yes	6.2	6.8	0.02	0.02	7.0	0.03	0.03	6.1	0.00	0.02	6.3	0.01	0.02
CYP1A2 inhibitor	Yes	2.4	2.1	0.02	0.02	2.6	0.01	0.02	2.3	0.01	0.01	2.7	0.02	0.02
CYP2B6 inhibitor	Yes	0.1	0.1	0.01	0.01	0.2	0.02	0.02	0.2	0.02	0.02	0.2	0.03	0.01
CYP2B6 inducer	Yes	2.2	1.5	0.05	0.01	2.4	0.02	0.04	2.0	0.01	0.02	1.8	0.03	0.03
Dipyridamole	Yes	0.7	0.7	0.01	0.01	0.7	0.00	0.01	0.8	0.01	0.01	0.7	0.00	0.02

Estrogen	Yes	1.8	2.2	0.03	0.03	2.7	0.06	0.03	2.1	0.02	0.01	3.0	0.08	0.04
Influenza vaccination	Yes	2.4	3.0	0.04	0.01	2.3	0.01	0.01	2.7	0.02	0.03	2.8	0.02	0.02
NSAID	Yes	12.0	15.9	0.11	0.06	17.5	0.16	0.04	13.2	0.04	0.06	18.7	0.19	0.05
Oral contraceptive	Yes	0.1	0.2	0.02	0.01	0.2	0.02	0.02	0.1	0.01	0.02	0.1	0.01	0.02
Renin angiotensin system antagonist	Yes	36.6	41.3	0.10	0.05	38.7	0.04	0.04	39.6	0.06	0.05	39.4	0.06	0.06
Statin	Yes	31.2	38.1	0.15	0.08	31.9	0.02	0.03	37.1	0.13	0.05	33.5	0.05	0.06
Thiazide diuretic	Yes	6.7	8.4	0.07	0.01	7.8	0.04	0.02	6.5	0.01	0.03	8.0	0.05	0.03
Vasodilator	Yes	19.7	16.8	0.07	0.06	19.0	0.02	0.04	18.7	0.03	0.04	18.3	0.03	0.06
Warfarin	Yes	4.0	2.9	0.06	0.06	3.3	0.03	0.03	3.4	0.03	0.03	2.2	0.10	0.03
<i>Acutely-occurring diseases</i>														
Cytomegaloviral disease	Yes	0.0	0.1	0.01	0.02	0.1	0.01	0.02	0.0	0.02	0.02	0.0	0.02	0.02
Helicobacter pylori	Yes	0.9	0.7	0.02	0.03	1.2	0.03	0.02	0.7	0.02	0.02	1.0	0.01	0.01
Herpes simplex	Yes	0.3	0.3	0.01	0.02	0.3	0.00	0.01	0.2	0.01	0.02	0.4	0.01	0.02
Fever	Yes	6.9	3.4	0.16	0.07	5.1	0.08	0.07	4.4	0.11	0.06	2.6	0.20	0.06
Gingival and periodontal disease	Yes	0.2	0.2	0.01	0.01	0.2	0.00	0.01	0.2	0.00	0.01	0.2	0.01	0.01
Infection, acute respiratory	Yes	10.8	12.5	0.05	0.05	12.0	0.04	0.04	9.8	0.03	0.05	12.8	0.06	0.04
Infection, serious (coded in other diseases**)†	Yes	26.5	18.0	0.21	0.08	23.1	0.08	0.07	20.5	0.14	0.07	17.1	0.23	0.12
Infection, urinary tract	Yes	21.0	14.1	0.18	0.07	18.5	0.06	0.04	16.0	0.13	0.06	14.0	0.19	0.10
Infectious and parasitic diseases, all other†	Yes	29.5	22.3	0.17	0.08	27.1	0.05	0.08	25.1	0.10	0.07	20.6	0.21	0.11
Pneumonia	Yes	14.5	7.0	0.25	0.10	10.4	0.12	0.09	9.0	0.17	0.09	6.2	0.27	0.10

SMD = standardized mean difference (vs. pantoprazole); WCSD = weighted conditional standardized difference (vs. pantoprazole); PPI = proton pump inhibitor; CMS = Centers for Medicare and Medicaid Services; COPD = chronic obstructive pulmonary disease; CAO = coronary artery occlusion; HIV = human immunodeficiency virus; AIDS = acquired immune deficiency syndrome; MI = myocardial infarction; ICD = implantable cardioverter-defibrillator; MAOI = monoamine oxidase inhibitor; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; NSAID = nonsteroidal anti-inflammatory drug

* not considered in the propensity score

** not already coded within *Infectious and parasitic diseases*

† baseline covariate, in addition to propensity score, included in the proportional-hazards model for the sensitivity analysis to control for potential residual imbalance in exposure groups

Supplemental Table II. High-level summary of other publications that have reported the association between clopidogrel + proton pump inhibitors (PPIs) and stroke, as a sole outcome

First author [PubMed identifier]	Design*	Setting	Exposure	N**	Outcome	Reported risk by PPI?	Result
van Boxel et al ¹ [20736935]	C	Netherlands; Dutch health insurance data; 2006-7	clopidogrel + PPI vs. clopidogrel	5,734	stroke (2°)	NO	aHR = 1.13 (0.78-1.65)
Bhatt et al ² [20925534]	RCT***	International; Clopidogrel and the Optimization of Gastrointestinal Events Trial (COGENT); phase 3 trial; 2008	(clopidogrel + omeprazole)+ASA vs. clopidogrel + ASA	1,876	ischemic stroke (2°) at 180 days	NO	log-rank p-value for difference in event rate between exposure groups = 0.43
Muñoz-Torrero et al ³ [21164357]	C	Spain; multicenter registry; 2003-9	clopidogrel + PPI vs. clopidogrel	519	ischemic stroke (2°)	NO	uRR = 1.9 (1.03-3.7)
Mahabaleshwarkar et al ⁴ [23362935]	C-C	US; Medicare elders (5% national sample); 2006-8	clopidogrel + PPI vs. clopidogrel	15,415	stroke (2°)	NO	aOR = 1.05 (0.86-1.28)
Tanaka et al ⁵ [22445597]	C-X	Japan; consecutive hospitalized persons; 2006-10	clopidogrel + ASA + PPI vs. ticlopidine + ASA + PPI	278	stroke (2°) at 30 days	NO	p-value for difference in event proportions between exposure groups = 0.19
Chitose et al ⁶ [22130313]	C	Japan; multicenter registry; 2008-9	clopidogrel + ASA + PPI vs. clopidogrel + ASA	187	ischemic stroke (sub of 1°)	NO	log-rank p-value for difference in event proportions between exposure groups = 0.60
Charlot et al ⁷ [20855802]	C	Denmark; national registry; 2000-6	clopidogrel + PPI vs. clopidogrel	6,753	stroke (2°) at 1 year	NO	aHR = 1.78 (1.47-2.16)
Simon et al ⁸ [21262992]	C	France; multicenter registry; 2005	clopidogrel + PPI vs. clopidogrel	1,453	stroke (sub of 1°) while inpatient	YES, but compared to a PPI-unexposed referent	aOR (clopidogrel + PPI vs. clopidogrel) = 0.33 (0.12-0.92) aOR (clopidogrel + omeprazole vs. clopidogrel) = 0.14 (0.03-0.67) aOR (clopidogrel + esomeprazole vs. clopidogrel) = 0.54 (0.14-2.16) aOR (clopidogrel + pantoprazole vs. clopidogrel) = 1.78 (0.36-8.83) aOR (clopidogrel + lansoprazole vs. clopidogrel) = incalculable
Kreutz et al ⁹ [20653354]	C	US; Medco Health Solutions benefits claims; 2005-6	clopidogrel +PPI vs. clopidogrel	6,828	stroke/TIA (sub of 1°) at 1 year	NO	aHR = 1.48 (1.08-2.01)
Ray et al ¹⁰ [20231564]	C	US; Tennessee Medicaid; 1999-2005	clopidogrel +PPI vs. clopidogrel	7,593	stroke (sub of 1°)	NO	aHR (overall) = 1.21 (0.82-1.78) aHR (if stented) = 0.97 (0.50-1.90)
Aihara et al ¹¹ [22234956]	C	Japan; multicenter registry; 2006-9	clopidogrel + ASA + PPI vs. clopidogrel + ASA	500	stroke (2°)	NO	aHR = 1.21 (0.48-3.19)

* C = cohort; C-C = case-control; C-X = cross-sectional; RCT = randomized controlled trial

** Persons in the antiplatelet + PPI arm

*** terminated

aHR = adjusted hazard ratio; ASA = aspirin; uRR = unadjusted rate ratio; US = United States; aOR = adjusted odds ratio; TIA = transient ischemic attack

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