

Appendix S1: List of *Helicobacter pylori* Treatment (HPT) regimes listed in the British National Formulary

- HPT containing clarithromycin regimes:** **EITHER:**
clarithromycin 250mg twice daily + metronidazole 400mg twice daily
+
One of the following:
esomeprazole 20mg twice daily
lansoprazole 30mg twice daily
omeprazole 20mg twice daily
pantoprazole 40mg twice daily
rabeprazole 20mg twice daily
- OR**
clarithromycin 500mg twice daily + amoxicillin 1g twice daily
+
One of the following:
esomeprazole 20mg twice daily
lansoprazole 30mg twice daily
omeprazole 20mg twice daily
pantoprazole 40mg twice daily
rabeprazole 20mg twice daily
- Clarithromycin free HPT regimes:**
amoxicillin 1g twice daily + metronidazole 400mg twice daily
+
One of the following:
lansoprazole 30mg twice daily
omeprazole 20mg twice daily

Appendix S2: Details of propensity score model

The propensity score was derived from a logistic regression model estimating the conditional probability of receiving a HPT regime containing clarithromycin given the following covariates:

Sex

Age

Smoking status

Alcohol status

Body Mass Index

Consulted GP in year before exposure

History of cardiovascular disease

History of heart failure

History of arrhythmia

History of hypertension

History of COPD

History of asthma

History of hyperlipidaemia

History of diabetes mellitus

History of cancer

History of NSAID use

History of oral corticosteroid use

History of antipsychotic use

History of antidepressant use

History of lipid lowering drug use

History of anticoagulant use

History of antiplatelet use

History of nitrate use

History of digoxin use

History of antiarrhythmic drug use

History of beta blocker use

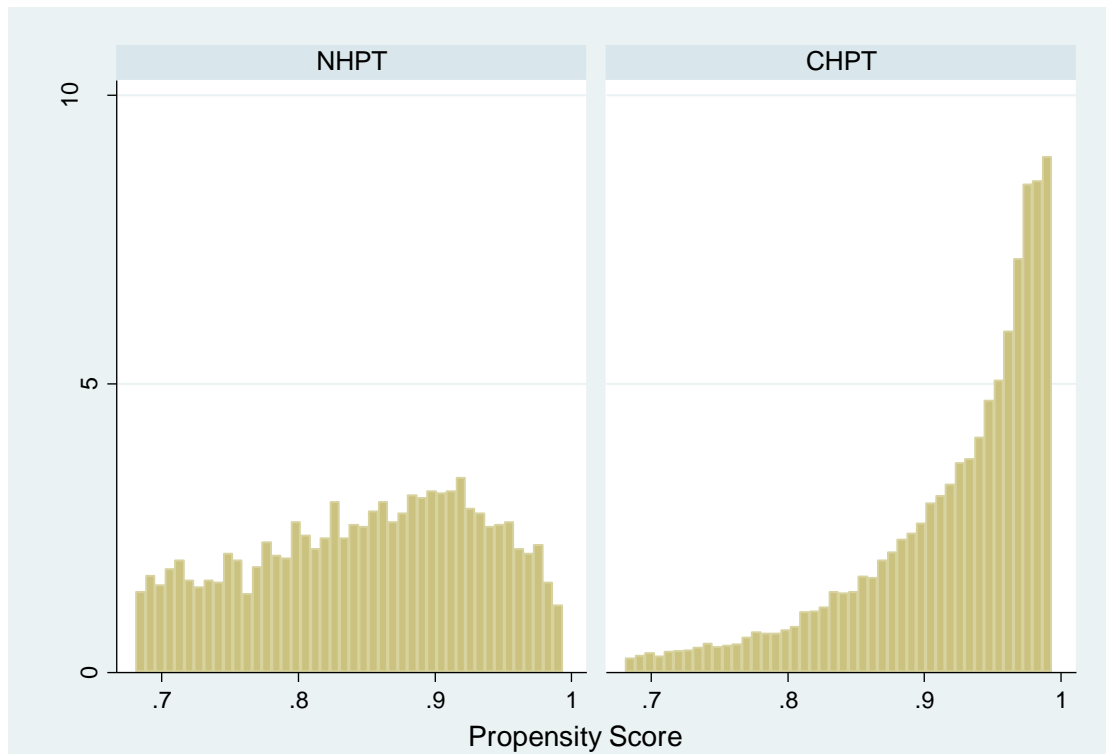
History of thiazide diuretic use

History of calcium channel blocker use

History of ACEI/ARB use

History of loop diuretic use

Appendix S3: The distribution of propensity scores by treatment group.



NHPT = Clarithromycin free *Helicobacter pylori* treatment. CHPT = *Helicobacter pylori* treatment containing clarithromycin.
Propensity score = Propensity to be prescribed CHPT given that *Helicobacter pylori* treatment is prescribed.

Appendix S4: Age bands for SCCS analysis

<20 years:	single band
20-30 years:	5 year bands
30-40 years:	2 year bands
40-80 years:	1 year bands
80-90 years:	2 year bands
>90 years:	single band

Appendix S5: Assumption of the SCCS method and our approaches to dealing with them

The SCCS method relies on three key assumptions. Firstly, recurrent events must be independent—that is, having a first event does not influence the likelihood of a second event. Although this does not hold for cardiovascular events, these events are sufficiently rare that restricting the analysis to the first incident event has been shown to be a valid approach⁶.

Secondly, the occurrence of an event should not alter the probability of subsequent exposure. For example, if a recent cardiovascular event was a contraindication to prescribing HPT, it would lead to a low rate of events in the period leading up to the first prescription of HPT and may artificially exaggerate the relative rate of events occurring in exposed versus unexposed periods. This potential bias can be overcome by removing a predefined period of time before exposure from all other unexposed (baseline) time⁸. In this study a two week period before exposure was removed from the baseline period. We repeated the analysis removing a two month period before exposure from the baseline as a sensitivity analysis to ensure that the two week period was sufficient to prevent bias in our analysis.

Thirdly, the event of interest must not censor the observation period—for example, if the event increases the likelihood of death—although there is some evidence that the method is robust to this assumption.⁷ Whether this assumption is fulfilled can be readily checked by measuring short term mortality after the event of interest.

Appendix S6: Baseline characteristics for cohort study including those dropped from the analysis due to missing or extreme propensity score

Characteristic	Clarithromycin containing HPT regime		Clarithromycin-free HPT regime	
	N	(%)	N	(%)
Sex				
Male	15809	(47.6%)	1536	(48.3%)
Female	17429	(52.4%)	1646	(51.7%)
Age				
0-40y	7967	(24%)	745	(23.4%)
40-50y	6812	(20.5%)	632	(19.9%)
50-60y	6778	(20.4%)	681	(21.4%)
60-70y	6315	(19%)	584	(18.4%)
70-80y	3972	(12%)	400	(12.6%)
>80y	1394	(4.2%)	140	(4.4%)
Smoking status				
non-smoker	13254	(39.9%)	1329	(41.8%)
current smoker	9578	(28.8%)	760	(23.9%)
ex-smoker	9938	(29.9%)	1060	(33.3%)
unknown	468	(1.4%)	33	(1%)
Alcohol status				
non-drinker	5473	(16.5%)	565	(17.8%)
ex-drinker	1460	(4.4%)	153	(4.8%)
current drinker (unknown quantity)	144	(0.4%)	15	(0.5%)
<2u/day	5711	(17.2%)	562	(17.7%)
3-6u/day	13723	(41.3%)	1299	(40.8%)
>6u/day	3424	(10.3%)	272	(8.5%)
unknown	3303	(9.9%)	316	(9.9%)
Body Mass Index				
normal	12282	(37%)	1174	(36.9%)
overweight	11287	(34%)	1078	(33.9%)
obese I	4630	(13.9%)	484	(15.2%)
obese II	1424	(4.3%)	137	(4.3%)
obese III	584	(1.8%)	53	(1.7%)
unknown	3031	(9.1%)	256	(8%)
Consulted GP in year before exposure	33137	(99.7%)	3171	(99.7%)
History of cardiovascular disease	5356	(16.1%)	460	(14.5%)
History of heart failure	926	(2.8%)	88	(2.8%)
History of arrhythmia	1774	(5.3%)	164	(5.2%)
History of hypertension	10396	(31.3%)	992	(31.2%)
History of COPD	2129	(6.4%)	212	(6.7%)
History of asthma	4610	(13.9%)	454	(16.3%)
History of hyperlipidaemia	5848	(17.6%)	529	(16.6%)
History of diabetes mellitus	4701	(14.1%)	444	(14%)
History of cancer	6092	(18.3%)	554	(17.4%)
History of NSAID use	2538	(7.6%)	212	(6.7%)

History of oral corticosteroid use	483	(1.5%)	50	(1.6%)
History of antipsychotic use	1136	(3.4%)	96	(3%)
History of antidepressant use	3973	(12%)	376	(11.8%)
History of lipid lowering drug use	3878	(11.7%)	481	(15.1%)
History of anticoagulant use	302	(0.9%)	49	(1.5%)
History of antiplatelet use	2798	(8.4%)	341	(10.7%)
History of nitrate use	842	(2.5%)	76	(2.4%)
History of digoxin use	186	(0.6%)	24	(0.8%)
History of antiarrhythmic drug use	75	(0.2%)	8	(0.3%)
History of beta blocker use	2855	(8.6%)	286	(9%)
History of thiazide diuretic use	2407	(7.2%)	250	(7.9%)
History of calcium channel blocker use	2624	(7.9%)	280	(8.8%)
History of ACEI/ARB use	3700	(11.1%)	421	(13.2%)
History of loop diuretic use	915	(2.8%)	91	(2.9%)
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Total	33238		3182	

Appendix S7: Results of the propensity score adjusted cohort analysis using Poisson regression for all outcomes including stratification by time from exposure.

	Patients (N)	Patient- years	Events (N)	Crude IRR (95% CI)			PS Adjusted IRR (95% CI)		
First MI									
HPT containing clarithromycin	26029	62118.98	174	0.89	(0.54-1.44)	p=0.62	0.75	(0.45-1.24)	p=0.26
Clarithromycin free HPT	2523	5688.98	18	1.00					
<i>Stratified Analysis by time since exposure</i>									
<i>0-90 days</i>									
HPT containing clarithromycin	26029	6251.51	23	1.11	(0.26-4.69)	p=0.10#	0.93	(0.22-3.98)	p=0.09#
Clarithromycin free HPT	2523	601.60	*	1.00			1.00		
<i>91-365 days</i>									
HPT containing clarithromycin	24741	17554.55	39	0.92	(0.33-2.56)		0.77	(0.27-2.17)	
Clarithromycin free HPT	2369	1649.42	*	1.00			1.00		
<i>1-2 years</i>									
HPT containing clarithromycin	22018	20519.04	67	0.61	(0.31-1.19)		0.51	(0.26-1.01)	
Clarithromycin free HPT	2047	1868.93	10	1.00			1.00		
<i>2-3 years</i>									
HPT containing clarithromycin	19108	17793.88	45	1.98	(0.48-8.12)		1.67	(0.40-6.94)	
Clarithromycin free HPT	1705	1569.03	*	1.00			1.00		
First Stroke									
HPT containing clarithromycin	26686	63847.36	68	0.38	(0.22-0.66)	p=0.001	0.47	(0.26-0.84)	p=0.01
Clarithromycin free HPT	2540	5746.98	16	1.00					
<i>Stratified Analysis by time since exposure</i>									
<i>0-90 days</i>									
HPT containing clarithromycin	26686	6411.09	6	0.57	(0.68-4.70)	p=0.56#	0.69	(0.08-5.82)	p=0.55#
Clarithromycin free HPT	2540	605.63	*	1.00			1.00		

91-365 days

HPT containing clarithromycin	25380	18019.87	20	0.62	(0.18-2.07)		0.75	(0.22-2.58)	
Clarithromycin free HPT	2386	1663.99	*	1.00			1.00		
1-2 years									
HPT containing clarithromycin	22608	21086.59	26	0.26	(0.12-0.55)		0.32	(0.14-0.70)	
Clarithromycin free HPT	2067	1891.22	9	1.00			1.00		
2-3 years									
HPT containing clarithromycin	24842	18329.82	16	0.46	(0.13-1.58)		0.57	(0.16-1.99)	
Clarithromycin free HPT	1725	1586.14	*	1.00			1.00		

First arrhythmia

HPT containing clarithromycin	26586	63581.67	95	0.43	(0.26-0.69)	p=0.001	0.37	(0.22-0.63)	p=0.001
Clarithromycin free HPT	2527	5702.77	20	1.00					

Stratified Analysis by time since exposure

0-90 days

HPT containing clarithromycin	26586	6368.35	18	1.70	(0.23-12.72)	p=0.02#	1.49	(0.19-11.26)	p=0.03#
Clarithromycin free HPT	2527	602.41	*	1.00					

91-365 days

HPT containing clarithromycin	25272	17943.67	23	1.06	(0.25-4.49)		0.93	(0.22-4.00)	
Clarithromycin free HPT	2373	1652.76	*	1.00					

1-2 years

HPT containing clarithromycin	22513	21000.53	26	0.2	(0.10-0.38)		0.17	(0.08-0.34)	
Clarithromycin free HPT	2050	1874.93	12	1.00					

2-3 years

HPT containing clarithromycin	19589	18251.12	28	0.48	(0.19-1.25)		0.42	(0.16-1.12)	
Clarithromycin free HPT	1712	1572.67	5	1.00					

All cause mortality

HPT containing clarithromycin	26827	64235.69	2621	1.09	(0.95-1.25)	p=0.22	0.96	(0.83-1.11)	p=0.59
Clarithromycin free HPT	2582	5851.81	219	1.00					

*Stratified Analysis by time since exposure**0-90 days*

HPT containing clarithromycin	26827	6445.37	163	0.87	(0.53-1.41)	p<0.001#	0.78	(0.48-1.27)	p<0.001#
Clarithromycin free HPT	2582	615.96	18	1.00			1.00		

91-365 days

HPT containing clarithromycin	25518	18119.60	359	0.96	(0.68-1.36)		0.86	(0.61-1.22)	
Clarithromycin free HPT	2427	1692.11	35	1.00			1.00		

1-2 years

HPT containing clarithromycin	22743	21217.86	327	1.06	(0.72-1.56)		0.95	(0.64-1.40)	
Clarithromycin free HPT	2101	1924.81	28	1.00			1.00		

2-3 years

HPT containing clarithromycin	19792	18452.86	1772	1.13	(0.95-1.34)		1.01	(0.85-1.21)	
Clarithromycin free HPT	1761	1618.92	138	1.00			1.00		

Cardiovascular mortality

HPT containing clarithromycin	11616	27729.71	416	1.05	(0.73-1.50)	p=0.80	0.93	(0.64-1.34)	p=0.69
Clarithromycin free HPT	1058	2234.28	32	1.00			1.00		

*Stratified Analysis by time since exposure**0-90 days*

HPT containing clarithromycin	11616	2787.91	30	0.67	(0.24-1.90)	p<0.001#	0.61	(0.21-1.73)	p<0.001#
Clarithromycin free HPT	1058	249.05	*	1.00			1.00		

91-365 days

HPT containing clarithromycin	11039	7832.93	57	1.21	(0.44-3.34)		1.10	(0.40-3.05)	
Clarithromycin free HPT	969	665.87	*	1.00			1.00		

1-2 years

HPT containing clarithromycin	9841	9180.91	43	0.57	(0.24-1.34)	0.52	(0.22-1.23)
Clarithromycin free HPT	810	730.63	6	1.00		1.00	

2-3 years

HPT containing clarithromycin	8553	7927.96	286	1.18	(0.73-1.90)	1.07	(0.66-1.75)
Clarithromycin free HPT	647	588.73	18	1.00		1.00	

IRR = Incidence rate ratio, CI = confidence interval, HPT = Helicobacter pylori Treatment MI = myocardial infarction, #LRT for interaction. *where there are less than 5 patients the exact number has been withheld in accordance with the confidentiality rules of the CPRD

Appendix S8: Results of the self-controlled case series analysis for first stroke.

	Patients (N)	Patient- years	Events (N)	Age adjusted IRR (95% CI)		
<i>Single risk window</i>						
Baseline	348	4560.9	306	1		
1 year post-exposure	348	350.48	40	1.33	(0.93-1.89)	p=0.11
<i>Multiple Risk window</i>						
Baseline	347	3945.24	246	1		
day 1-30 post-exposure	348	30.13	*	1.27	(0.4-4)	p=0.68
day 31-90 post-exposure	348	59.61	6	1.27	(0.56-2.89)	p=0.57
day 91-365 post exposure	345	261.66	31	1.47	(0.99-2.19)	p=0.06
year 1-2 post-exposure	326	321.48	35	1.47	(1.01-2.13)	p=0.04
year 2-3 post-exposure	301	293.34	25	1.12	(0.73-1.72)	p=0.6

All IRRs are age adjusted and derived from conditional Poisson regression. MI = myocardial infarction, CI = confidence interval, IRR = incidence rate ratio. Median follow up was 14.0 years. *where there are less than 5 patients the exact number has been withheld in accordance with the confidentiality rules of the CPRD

Appendix S9: Results of the self-controlled case series analysis for the outcomes of first MI in patients with linked HES outcome dates for multiple risk window analysis.

	Patients (N)	Patient- years	Events (N)	Age adjusted IRR (95% CI)		
Primary Outcome: First MI (median follow up 13.6y)						
Baseline	359	4111.38	250	1		
day 1-30 post-exposure	359	30.19	8	3.77	(1.85-7.68)	p<0.001
day 31-90 post-exposure	357	59.21	7	1.67	(0.78-3.58)	p=0.18
day 91-365 post exposure	352	260.83	21	1.13	(0.72-1.79)	p=0.59
year 1-2 post-exposure	335	318.93	32	1.40	(0.99-2.06)	p=0.08
year 2-3 post-exposure	305	296.07	31	1.49	(1.01-2.20)	p=0.04

All IRRs are age adjusted and derived from conditional Poisson regression. MI = myocardial infarction, CI = confidence interval, IRR = incidence rate ratio